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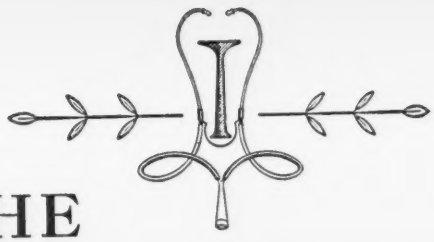

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OCTOBER
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VOL LVIII
NO X

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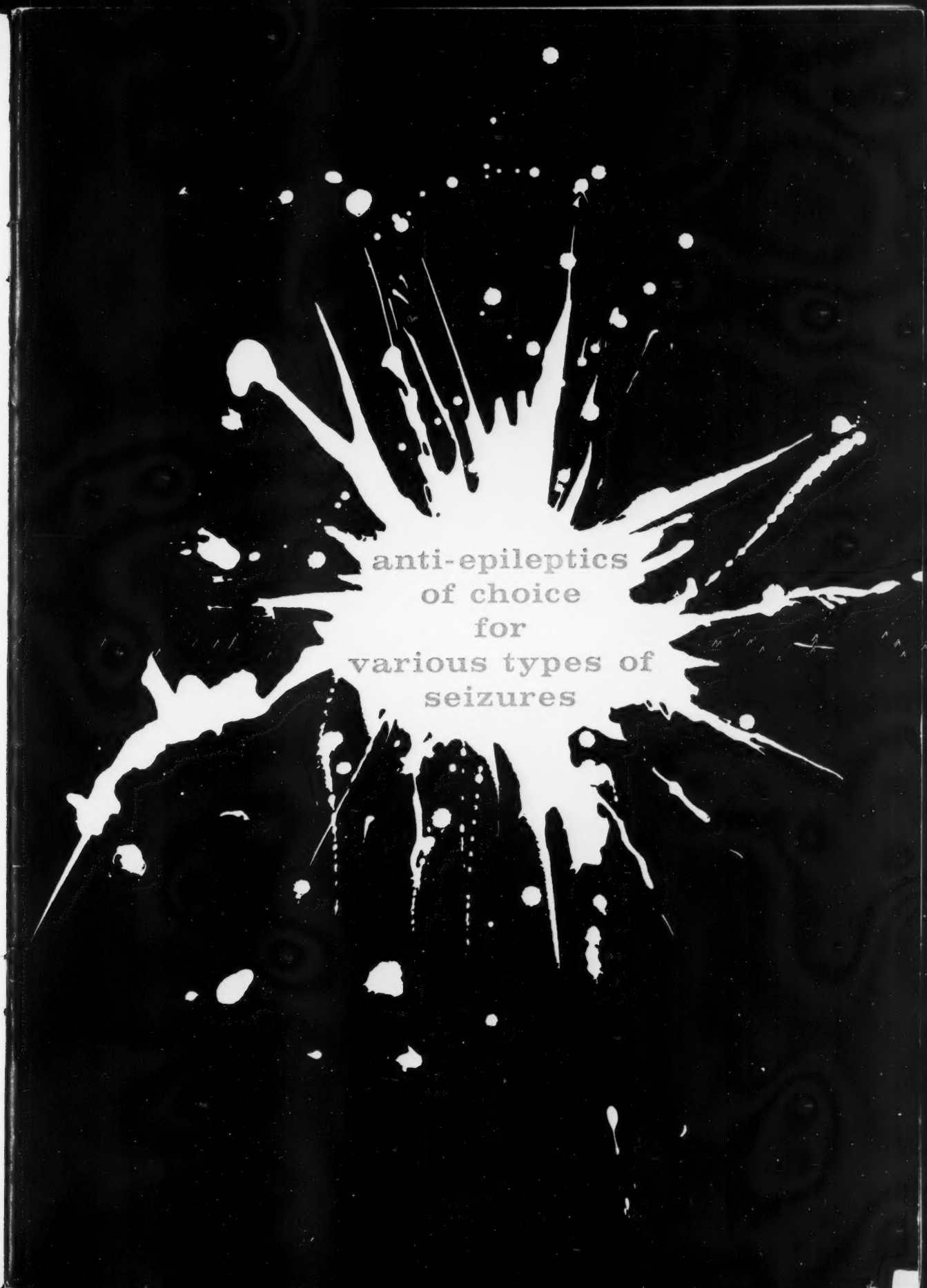
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THE JOURNAL
of the
KANSAS MEDICAL SOCIETY

Volume LVIII | OCTOBER, 1957 | Number 10

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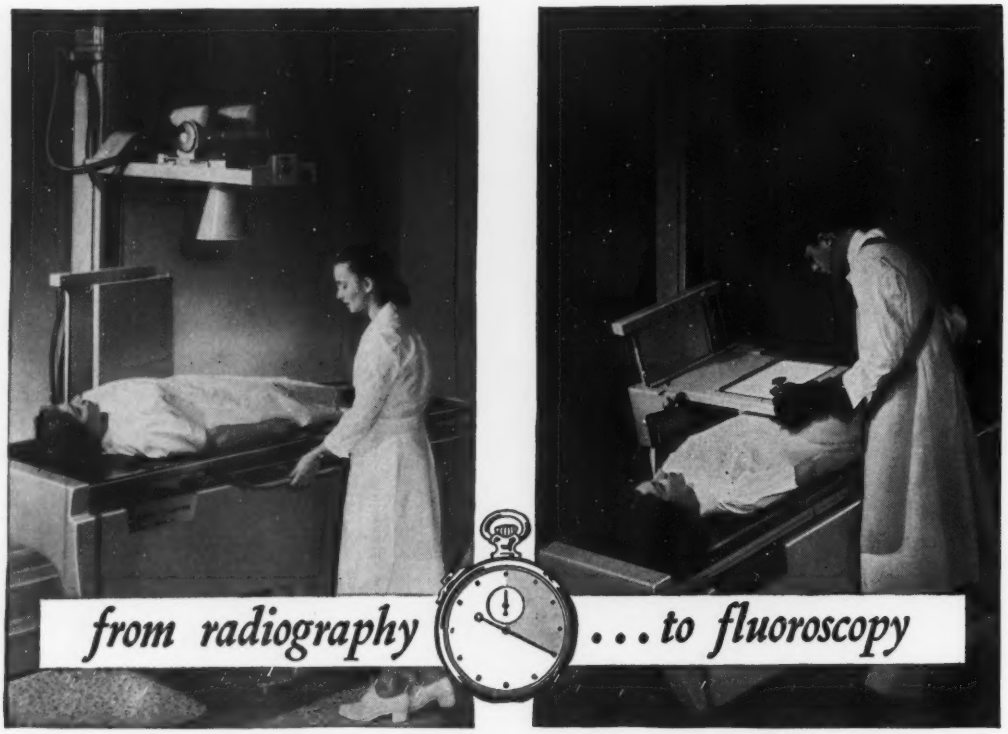

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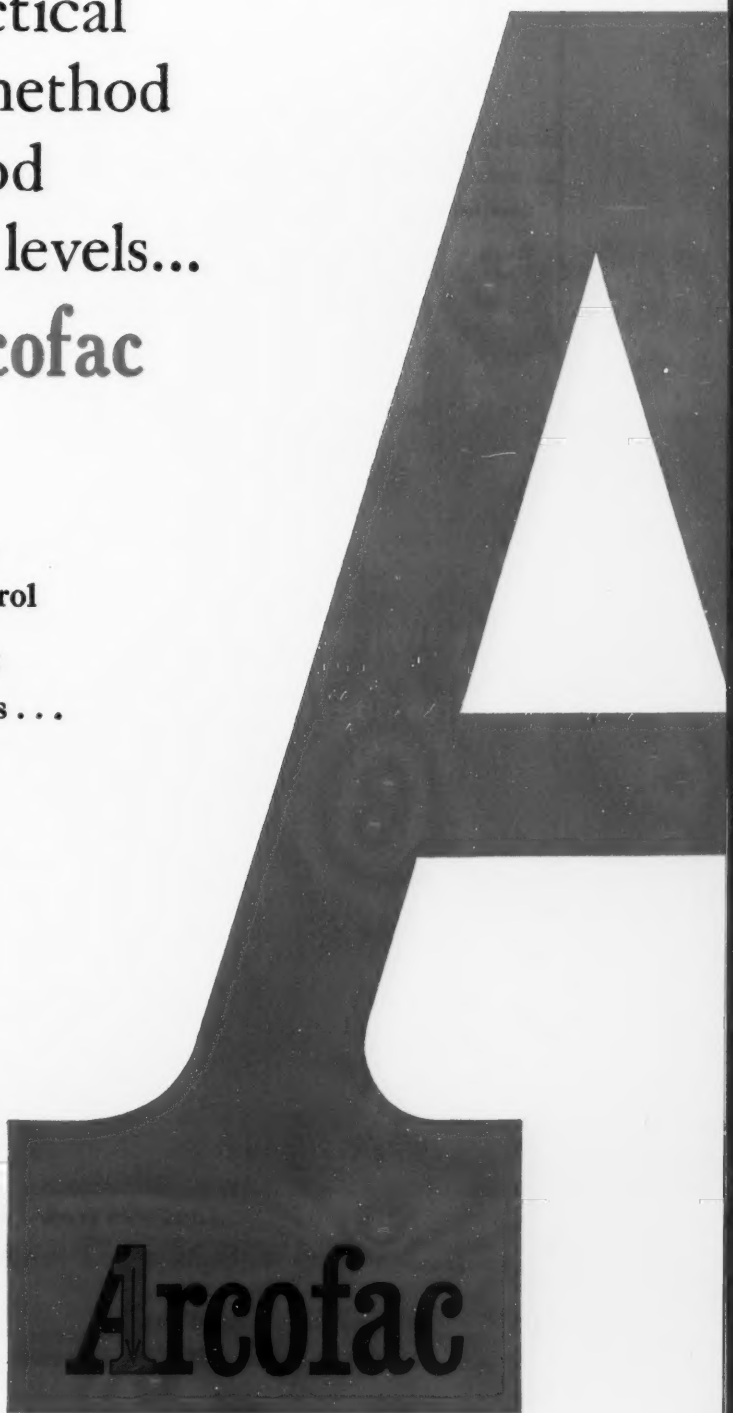

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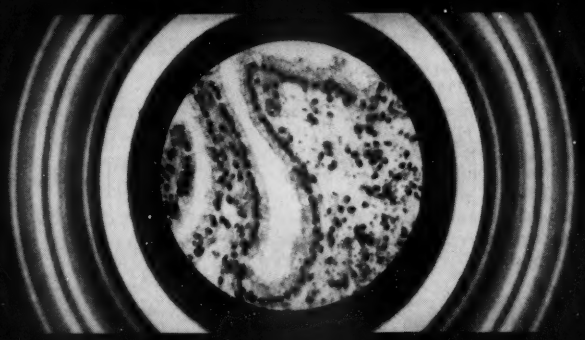

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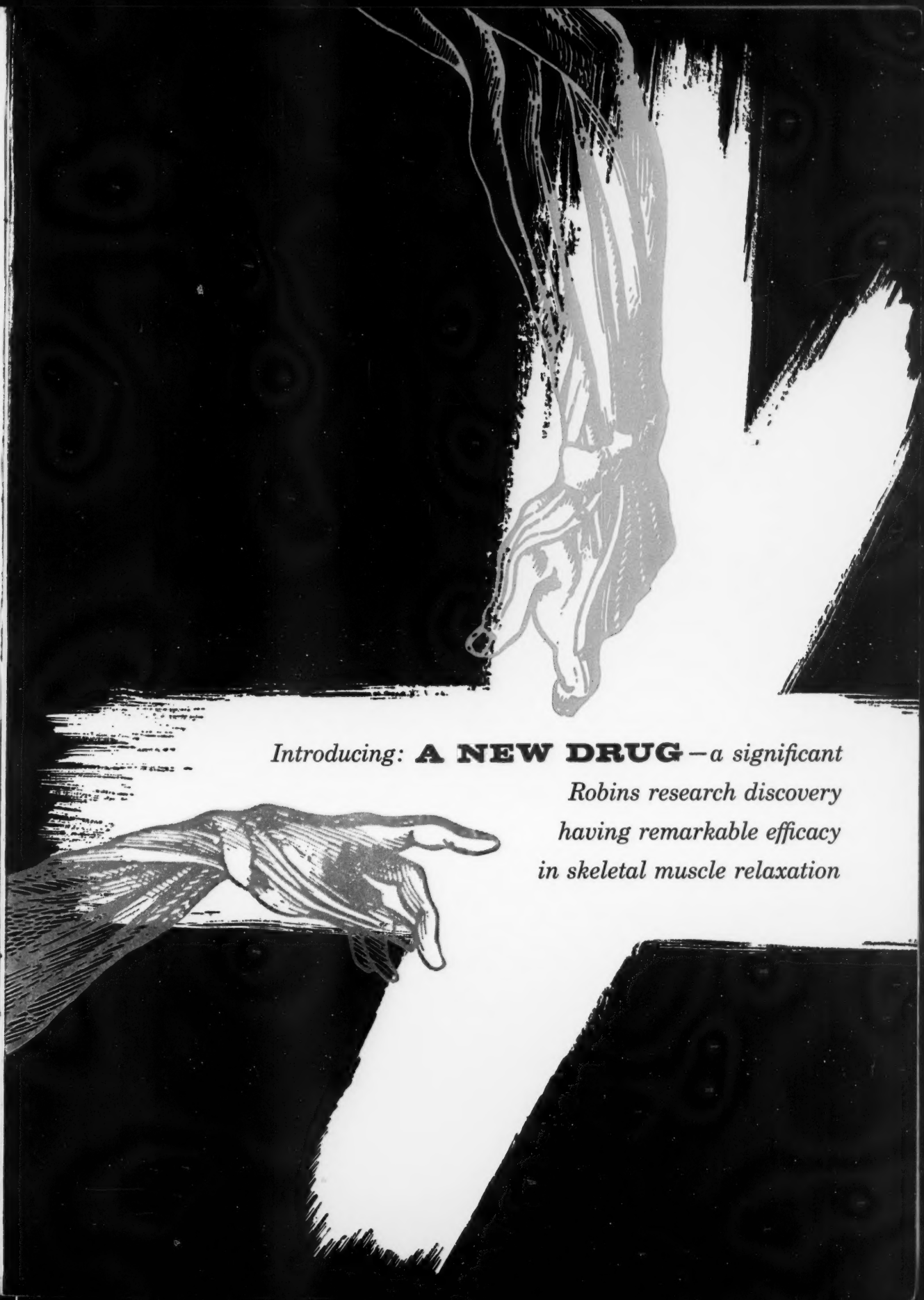

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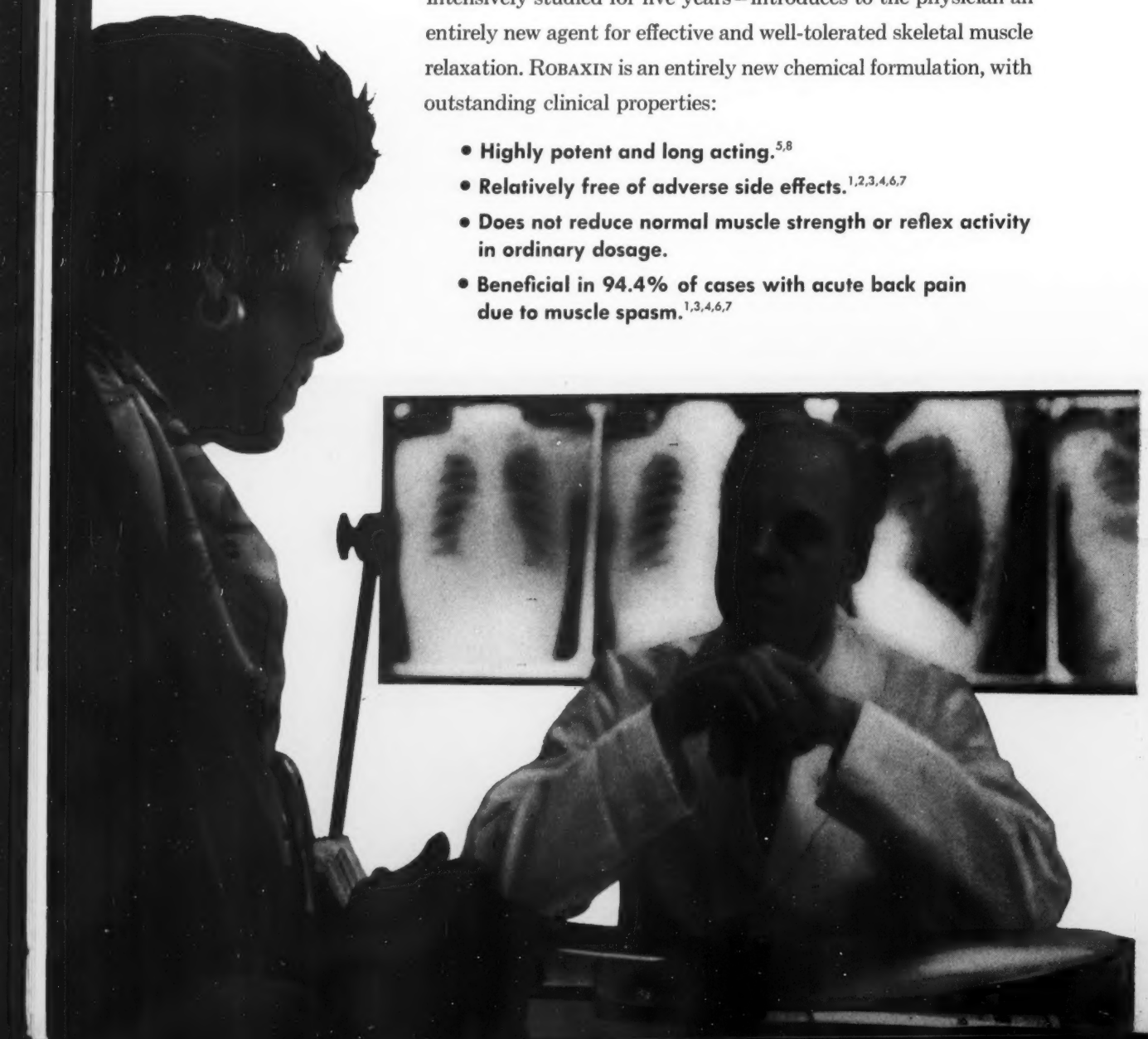

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Disease entity	*No. of Cases*	*Duration of Treatment*	*Dose per day (divided)*	*Response*				*Side Effects*
				Marked	*Mod.*	*Slight*	*Neg.*	
Acute back pain due to *								
(a) Muscle spasm secondary to sprain	18	2-42 days	3-6 Gm.	17	1	0	0	None, 16; Dizziness, 1; Slight nausea, 1.
(b) Muscle spasm due to trauma	13	1-42 days	2-6 Gm.	8	1	3	1	None, 12; Nervousness, 1.
(c) Muscle spasm due to nerve irritation	5	4-240 days	2.25-6 Gm	4	1	0	0	None, 5.
(d) Muscle spasm secondary to discogenic disease and postoperative orthopedic procedures	30	2-28 days	1.5-9 Gm.	24	3	0	3	None, 25; Dizziness, 1; Lightheadedness, 2; Nausea, 2.*
Miscellaneous (bursitis, torticollis, etc.)	6	3-60 days	4-8 Gm.	6	0	0	0	None, 6.
TOTAL	72			59	6	3	4	

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References:

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8. Truitt, E. B., Jr., and Little, J. M.: J. Pharm. & Exper. Therap. 119:161, 1957.

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New York, Aug. 15 (AP) Laboratory tests on e foreign exchange student arrived Aug. 8 show they victims of Asiatic flu, the health department repo today. The eight arrived plane from Europe.

Twenty-nine other stud suffering from influenza rived Tuesday from Rot dam on the ship Arosa Sky. One, Nicholas Memmos, Greek exchange student, mo yesterday. Six of these stu dents were released today the others are to be re tomorrow. It has not termined whether died from Asiatic

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Asian Flu: the Outlook

Asian influenza will hit the U.S. this fall before mass immunization can be effective, and the nation faces an epidemic which may strike 15 million to 30 million people. The disease is relatively mild (in no way comparable to the killing "Spanish flu" of 1918-19), and is likely to cause only a small number of deaths among the feeble young and enfeebled old. But it may compel 10% to 20% of the population in affected areas to tak thus

W quie a co pect Ser pop

Pea vac izat flov the ority States

U.S. Fighting Asia

The War On Asiatic Flu

There's cause for concern about Asiatic flu, but scientists and public health officials see no reason for anyone to panic.

First shipments of the vaccine against the new influenza strain have arrived in Chicago, setting off a flood of telephone calls from worried patients to doctors, and from doctors to drug suppliers. This is a norm pattern of mass fear and is understan The of the

Even though Salk vaccine priorities were necessary, the regulation produced administrative headaches, public complaints and probably a gray, if not a black market. When regulation i invoke it. would h

PUBLIC HEALTH

Influenza May S

➤ INFLUENZA, one of the most unpredictable of communicable diseases, is resting "on cat feet" across the nation right now. It has already struck once this year in mild epidemic form at an Air Force base in Colorado. When and how severely it will strike again is a perennial riddle to public health authorities.

It will probably not lie dormant for the rest of the winter months. At the least there will be sporadic outbr throughout the country. If ditions occur, it could sw

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NZA EPIDEMIC

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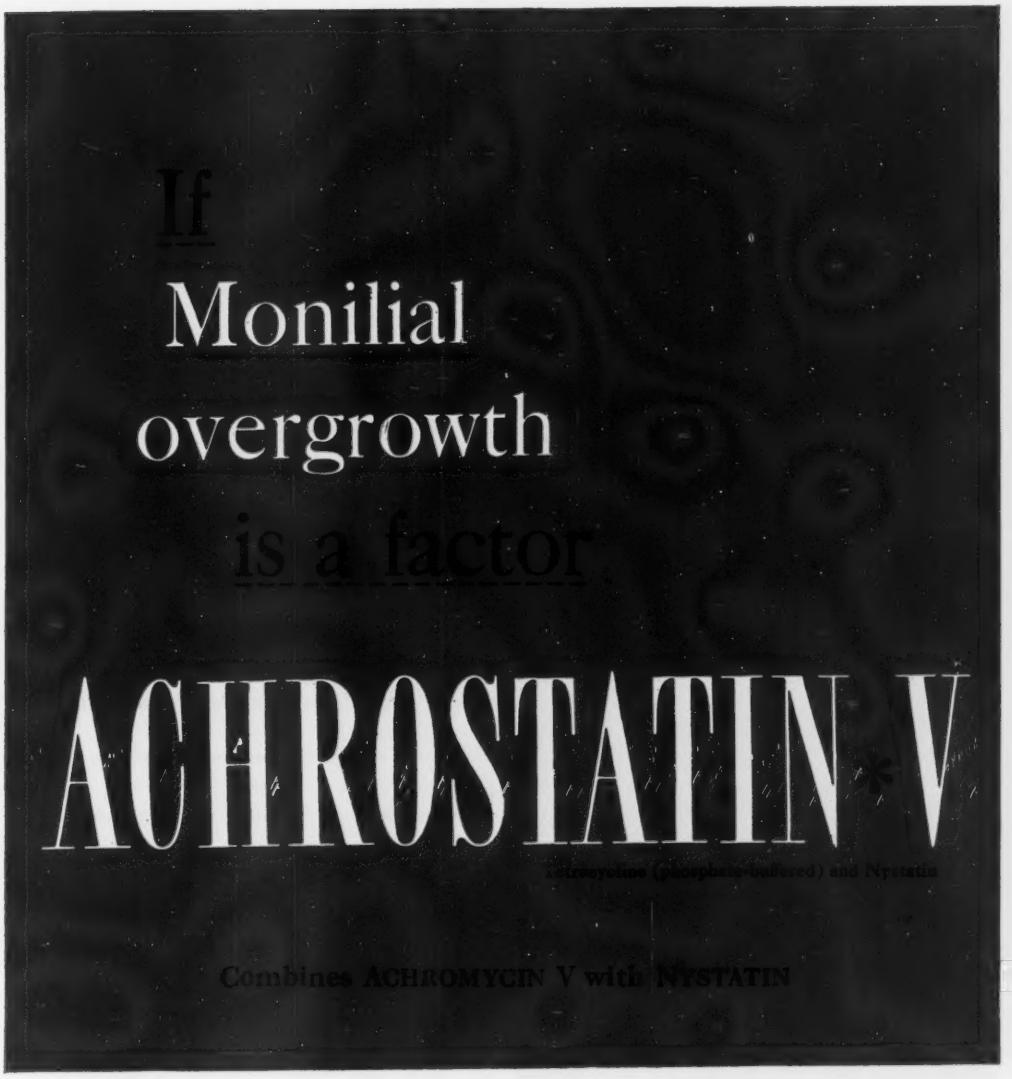

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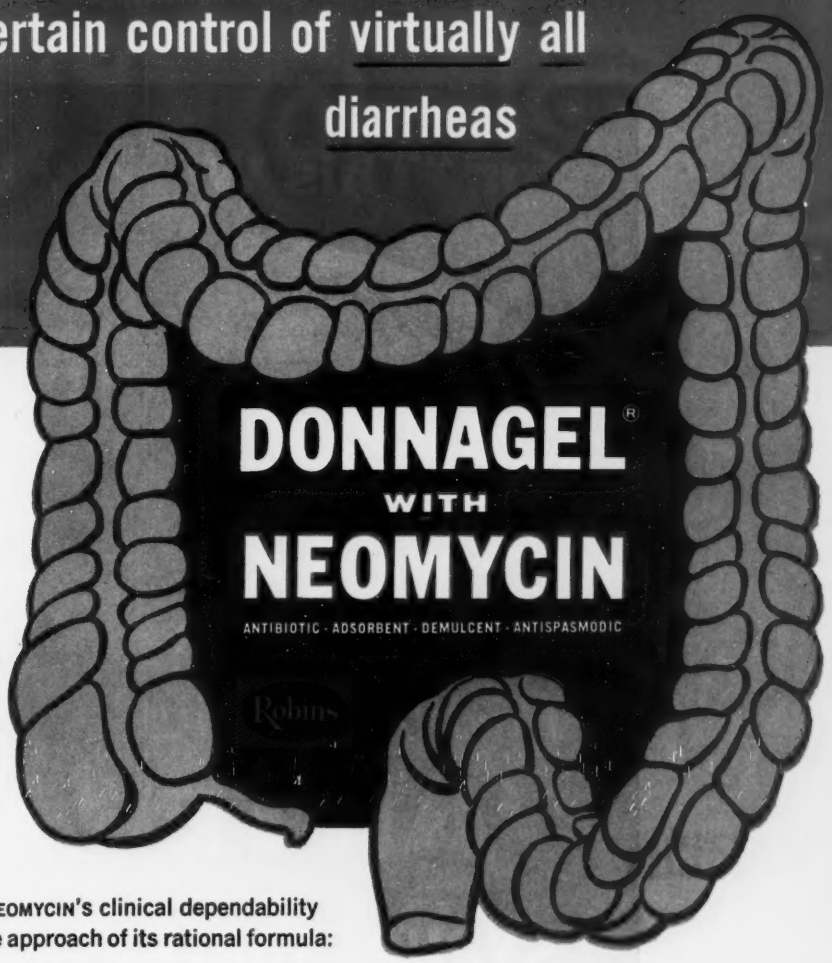

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Neomycin is an ideal antibiotic for enteric use: it is effectively bacteriostatic against neomycin-susceptible pathogens; and it is relatively non-absorbable.

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COMPONENT in each 30 cc. (1 fl. oz.)	ACTION	BENEFIT
Neomycin base, 210.0 mg. (as neomycin sulfate, 300 mg.)	antibiotic	Affords effective intestinal bacteriostasis.
Kaolin (6.0 Gm.)	adsorbent, demulcent	Binds toxic and irritating substances. Provides protective coating for irritated intestinal mucosa.
Pectin (142.8 mg.)	protective, demulcent	Supplements action of kaolin as an intestinal detoxifying and demulcent agent.
Dihydroxyaluminum aminoacetate (0.25 Gm.)	antacid, demulcent	Enhances demulcent and detoxifying action of the kaolin-pectin suspension.
Natural belladonna alkaloids: hyoscyamine sulfate (0.1037 mg.) atropine sulfate (0.0194 mg.) hyoscine hydrobromide (0.0065 mg.)	antispasmodic	Relieves intestinal hypermotility and hypertonicity.
Phenobarbital (¼ gr.)	sedative	Diminishes nervousness, stress and apprehension.

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INDICATIONS: DONNAGEL WITH NEOMYCIN is specifically indicated in diarrheas or dysentery caused by neomycin-susceptible organisms; in diarrheas not yet proven to be of bacterial origin, prior to definitive diagnosis. Also useful in enteritis, even though diarrhea may not be present.

SUPPLIED: Bottles of 6 fl. oz. At all prescription pharmacies.

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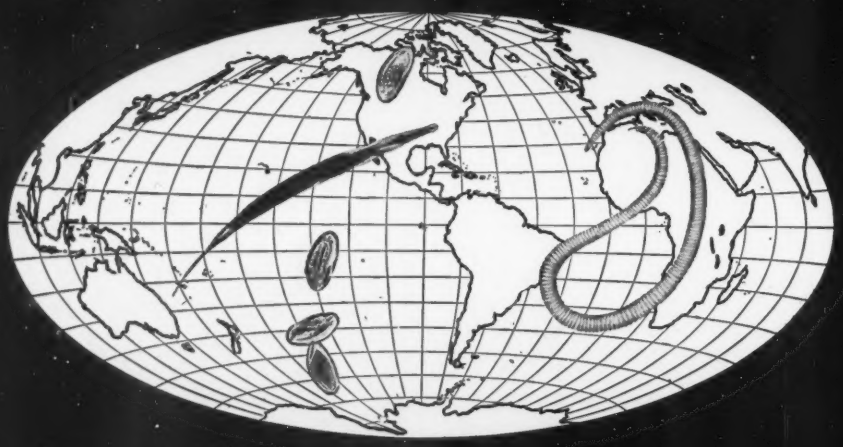

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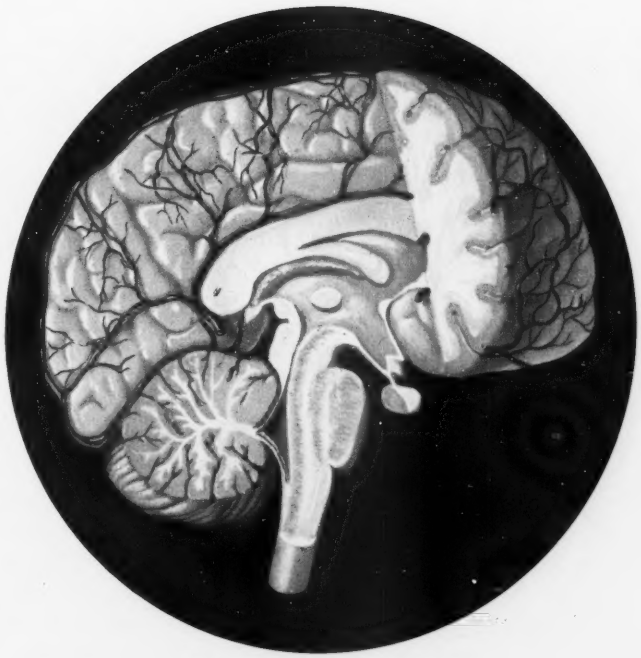

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WITHOUT IMPAIRING MENTAL OR PHYSICAL EFFICIENCY

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Supplied: 400 mg. scored tablets
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Usual dosage: One or two 400 mg. tablets t.i.d.

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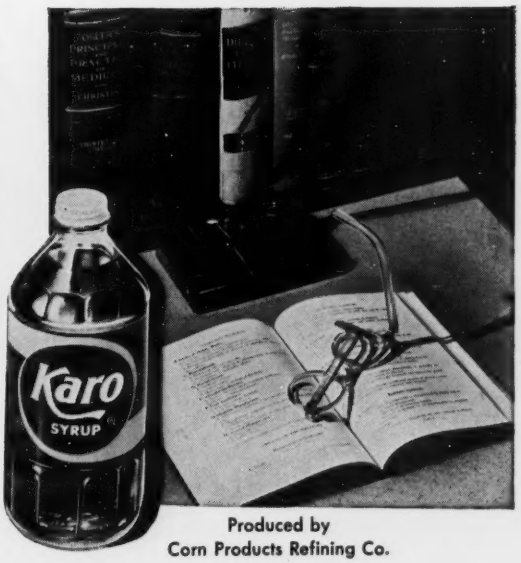

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» *Milligram for milligram, DIMETANE potency is unexcelled.* DIMETANE has a therapeutic index unrivaled by any other antihistamine—a relative safety unexceeded by any other antihistamine. DIMETANE, even in very low dosage, has been effective when other antihistamines have failed. Drowsiness, other side effects have been at the very minimum.

» unexcelled antihistaminic action

Diagnosis	No. of Patients	Response				Side Effects
		Excellent	Good	Fair	Negative	
Allergic rhinitis and vasomotor rhinitis	30	14	9	5	2	Slight Drowsiness (3)
Urticaria and angioneurotic edema	3	1	1	1		Dizzy (1)
Allergic dermatitis	2		1	1		Slight Drowsiness (2)
Bronchial asthma	1		1			
Pruritus	1		1			
Total	37	15	13	7	2	Drowsiness (5) Dizzy (1) 16.2%

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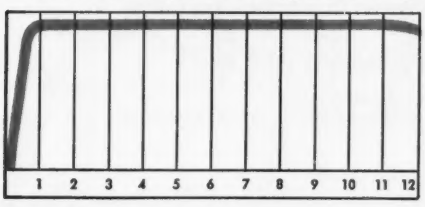
DIMETANE IS PARABROMDYLAMINE MALEATE – EXTENTABS 12 MG., TABLETS 4 MG., ELIXIR 2 MG. PER 5 CC.

a blanket of allergic protection, covering 10-12 hours—with just one Dimetane Extentab » *DIMETANE Extentabs protect patient for 10-12 hours on one tablet.*



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• allays bronchial spasm • liquefies tenacious secretions • suppresses allergic manifestations

The ingredients of Hydryllin Compound are proportioned to provide high therapeutic response.

Each 4 cc. (one teaspoonful) contains:

Aminophyllin	32.0 mg.	Chloroform	8.0 mg.
Diphenhydramine	8.0 mg.	Sugar	2.8 Gm.
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when anxiety and tension "erupts" in the G. I. tract...

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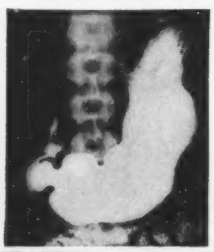

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Dosage: 1 tablet t.i.d. at mealtime. 2 tablets at bedtime. *Supplied:* Bottles of 100, 1,000.

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Special Liver-Stomach Concentrate, Lilly (containing Intrinsic Factor)	*300 mg.*
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Vitamin B_{12} Activity Concentrate, N.F.	*15 mcg.*
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Potent 'Trinsicon' offers complete and convenient oral therapy; provides therapeutic quantities of all known hematinic factors. Just two Pulvules 'Trinsicon' daily produce a standard response in the average uncomplicated case of pernicious anemia (and related megaloblastic anemias) and provide at least an average dose of iron for hypochromic anemias, including nutritional deficiency types.

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Hospital Insurance Ideals

The American Hospital Association today said it believed individuals would have the best type of hospitalization prepayment coverage "when extensions of coverage for prolonged illness are supplementary to and integrated with adequate coverage of short-term illness."

This statement was part of Recommended Benefits of Prepaid Hospitalization Plans, a guide published in the August 16 issue of *Hospitals, Journal of the American Hospital Association.* The document points out that "there are groups for which it is difficult to make benefits sufficiently inclusive, and certain health services which are not generally available."

The guide urges prepaid health care plans to "encourage the use of outpatient facilities, long-term care facilities, and home care programs when necessary health care can be provided in or through such facilities at less cost than inpatient care in a general or special short-term hospital."

It observes that "While payment for necessary health care is primarily the responsibility of the individual or the family unit, government and the community have a legitimate responsibility to provide or to assist in paying for necessary health care for those people who are unable to finance it themselves."

Necessary health care is defined as "the total diagnostic and treatment services made available through hospitals and related institutions, which are required for the proper care of acute and prolonged illness." The guide says, "Such health care should be made available for as long as the responsible physician may prescribe in accordance with sound medical practice."

Desirable benefits of prepayment for necessary care in general hospitals should include, according to the guide, "the requisite days of care in a multiple bed accommodation and the unrestricted use of the special services provided through the hospital."

A three-day cold costs the average person $25. And, says the Kansas State Board of Health, colds cause 50 to 60 per cent of all absences from work.

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PHENAPHEN® PLUS
Phenaphen Plus is the physician-requested combination of Phenaphen, plus an antihistaminic and a nasal decongestant.
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Volume LVIII **OCTOBER, 1957** **No. 10**

Therapeutic Syndromes

Are Doctors Outsmarting Themselves Therapeutically?

JESSE D. RISING, M.D., ***Kansas City***

"Man is the only creature that is capable of disliking the creation . . . in his ardor to reform and recolor what is intrinsically not so good, he tends to overlook what is intrinsically not so bad."[1]

He "is the one creature who can significantly alter himself and his environment to suit his private tastes . . . who can know very much about himself . . . who can dodge many harsh and dangerous exactions of Nature only to run foul of harsh and dangerous devices of his own manufacture."[2]

"When Nature gave him a brain and with it the unprecedented privilege of contributing to the arrangement of his own life, she included the less enviable capacity of suffering for his own mistakes."[3]

Man's tampering with the balance of nature—even with the best of intentions—has very commonly led to unhappy results: English sparrows were imported to save the elms from measuring worms only to upset avian ecology and displace many songbirds. Mongooses were brought into Jamaica for the purpose of controlling the rats which took a toll of the local agriculture, only to have the "saviours," when they ran out of rats, turn upon birds, lizards, and other small animals that contributed to the control of insects with the result that a host of destructive insects was unleashed to devastate the crops.

Physicians and engineers have contributed their share to the imbalance of nature and have made it possible for vast numbers of human creatures to inhabit this planet, often in dense concentrations. In recent years physicians have even found it possible to apply specific therapy to the cure of disease—not only preventive and palliative measures—but the effect has not invariably been salubrious, and it has developed that the cure may not always be an unmixed blessing but may, indeed, be worse than the disease.

It would perhaps be out of place to discuss at this juncture the ethics and philosophy of the physician's interference with natural processes and the balance of nature. Perhaps, from our present standpoint, it would be appropriate, on the other hand, to pause and review some of the basic philosophy of therapeutics. We must always keep uppermost in our minds the fact that any medication is a calculated risk and must be viewed as no better than the lesser of two evils. The present trend seems to be for scientists to accumulate facts faster than understanding. This is probably inevitable, but we are under an obligation to exert every effort to bring understanding as near abreast the facts as possible.

In addition, we must recognize the effects of medicine on human genetics, realizing that "the long-term influence of our modern advances in medicine and of all our artificial aids to life must gradually decrease the biological fitness of the population. This happens by the ever increasing accumulation of all sorts of mutations that, under more severe conditions, would have been eliminated. Since new mutations keep occurring in every generation and

Presented at the annual meeting, Kansas Chapter, American Academy of General Practice, Wichita, May 6, 1957.

are thereafter handed down unless some descendant dies of his disability, these mutations will tend to accumulate until the population is bearing as great a load of them as can be kept alive by its greatly enlarged cohorts of doctors, exercising their best medical skill and working overtime. Moreover, the more we add to the naturally occurring mutations by producing others by means of atomic radiation or medical x-rays, the sooner this eventuality will materialize."[4]

It is imperative that physicians remember that even the best medicine, under the best circumstances, is at best the lesser of two evils. We all recognize, of course, that drugs have toxic actions and physiologic side effects; these are often predictable on the basis of the pharmacologic actions of the drug or as hypersentivity reactions. Of increasing interest in recent years are reactions that cannot, in our present state of knowledge, be placed in either of these groups. These reactions present the appearance of actual disease states, mimicking or reproducing with variable degrees of accuracy diseases which have been known for some time. The following are a few that have, without any effort to search the literature, come to the attention of one general practitioner pursuing, not too diligently I fear, the journals which an average physician might be expected to have available even in a rural office.

Hydralazine *(Apresoline)*

Perhaps the most interesting example of this situation is what is sometimes called the hydralazine syndrome. This is in reality two diseases—or appears to be so—the first being rather typical rheumatoid arthritis complete with all of the expected laboratory findings. The more severe form, and the more dramatic one, is less common and is, to all intents and purposes, identical with acute disseminated lupus erythematosis, including the presence of a biologic false-positive reaction for syphilis and positive lupus erythematosis cell preparations.[5-10] The only apparent difference between typical acute disseminated lupus and the severe form of hydralazine syndrome is the fact that patients usually get better immediately when the drug is discontinued, but this is not invariably true as some patients have required treatment with ACTH and cortisone.

This syndrome can apparently be produced with great efficiency if one really puts his mind to the job. It seems that we can expect to produce hydralazine syndrome in 8 to 10 per cent of patients who are treated intensively for several months.

Adrenal Cortical Hormones

Typical peptic ulcers are so commonly produced by cortisone, hydrocortisone, prednisone, and prednisolone that manufacturers have recently begun to incorporate antacids in preparation of some of these hormones. Incidentally, this is a pharmacologically irrational approach to the problem which undoubtedly tends to give the physician a false sense of security without materially affecting the incidence of the complication, and it is therefore to be deplored.

The outstanding atypical feature of this type of peptic ulcer is that it is frequently asymptomatic until the patient develops a massive hemorrhage or perforation. The perforation may actually cause relatively few symptoms, and the patient may have extensive peritonitis before there are indications of illness. This is indeed a high price to pay for the benefits to be derived from the treatment, especially if the condition calling for use of the hormone be a relatively benign one, as is often the case.[11]

Euphoria is often one of the outstanding results of corticoid therapy and would be a welcome one in many instances were it not for the fact that it indicates affective changes which may, and not infrequently do, lead to frank psychotic reactions, mimicking the well-known manic-depressive psychoses. The psychosis may be characterized by elation or mania on one hand or severe depression or melancholia on the other. Some patients have been reported to develop typical schizophrenic behavior patterns while under corticoid therapy.

More than a few patients have had typical grand mal epilepsy while being treated with corticoids, and, while patients with abnormal electroencephalographic patterns seem to be more frequent victims of this type of reaction, a normal electroencephalogram is no guarantee that the patient will escape. Grand mal seizures seem to be especially frequent among children.[11, 12]

Corticoids are commonly used in the treatment of arthritic conditions, and one must constantly be alert to the fact that the hormones are prone to cause osteoporosis. This complication can most often be expected in elderly individuals and may materially contribute to the worsening of their orthopedic problems. The weakening of the bones may even go so far as to produce spontaneous fractures in postmenopausal women.

A source of trouble that has often been overlooked is the shortening of coagulation time in patients who are on corticoid therapy, but reports indicate that there is a high incidence of thromboembolism, including pulmonary embolism, in patients being treated with adrenal cortical steroids.[13, 14]

Reserpine and Rauwolfia Products

Even the youngest practitioner of medicine must certainly remember when Rauwolfia and its products were introduced as extremely safe, if somewhat

mild, antihypertensive drugs. At that time it was recognized that these drugs had ataractic or tranquilizing properties, and the literature was full of suggestions that here at last was an extremely safe calmative agent to take the place of phenobarbital. I sincerely hope that no practitioner now holds this prejudice, for it is certain that reserpine is one of the most dangerous of the tranquilizers—so dangerous that it has really very few indications.

Soon after introduction of the drug into human therapeutics, it was recognized that the incidence of peptic ulcer in patients under treatment with it was far in excess of what one could reasonably expect on the basis of chance. The pharmacology of the drug would, indeed, lead one to expect that this complication might result, for it has almost precisely the opposite effects of vagotomy. We now know from human and animal experiments that both oral and parenteral reserpine increase secretion of gastric acid, and there seems to be little doubt that the drug can precipitate peptic ulcers.[15]

Psychic depression is a relatively common side effect of reserpine therapy, and the literature is burdened with reports of severe psychotic reactions. Most of them resemble the depressive phase of manic-depressive psychosis, but some are characterized by agitation or paranoia with suicidal tendencies. Numerous suicides have been reported, and many physicians have knowledge of unreported cases. We can only speculate about the frequency of severe psychologic reactions, but when one considers the documented incidence of major psychoses and less severe emotional reactions as compared with the drug's inefficiency as an antihypertensive agent, one is reluctant to accept it as a routine medication for treatment of hypertension.[16, 17, 18]

In addition to this we are presented with reports of edema and congestive heart failure being precipitated by reserpine (and alseroxylon) in patients with hypertension but without a previous history of decompensation. These patients developed ankle edema shortly after institution of therapy, and some developed exertional dyspnea and basilar rales. The other disturbing feature is that only one patient in five had significant lowering of blood pressure. None of the patients improved until the drug was discontinued, but all responded promptly after it was withdrawn.[19]

To make matters worse, we have evidence that Rauwolfia can apparently be blamed for production of ventricular premature contractions in patients with organic heart disease and high blood pressure.[20]

Mecamylamine *(Inversine)*

The quest for drugs useful in treatment of hypertension goes on, and it is not surprising that ganglionic blocking agents are being explored extensively. One of the promising new drugs is mecamylamine which, because it is a secondary rather than a quaternary amine, penetrates cells more efficiently than the other ganglionic blocking agents and is consistently and completely absorbed from the gastrointestinal tract. The improved absorption would be a great boon, but it has been postulated that the very feature responsible for this pharmacologic triumph may permit the drug to enter cells in the central nervous system with something less than happy results.

Many patients have been observed to develop neurotic reactions characterized by anxiety or depression (or a mixture of these symptom complexes) as a result of mecamylamine therapy. Patients more severely affected have developed a neurological reaction that is reminiscent of chorea. Some have had jerking and intention tremor and have impressed observers as having a condition similar to Huntington's chorea, while others have had queer, purposeless, irregular movements of the extremities, face, and body which are more characteristic of Sydenham's chorea. Slurred speech, dysphagia, and dysarthria have been reported, and it must be difficult, when these symptoms are combined with intention tremor, to differentiate the condition from multiple sclerosis. In addition, some patients have exhibited grand mal epilepsy.[21]

There is a probability that mecamylamine can produce a major psychosis in addition to the neurotic and motor reactions noted above.[22]

Hexamethonium

No one who has used ganglionic blocking agents in the treatment of severe hypertension has been impressed by the benign nature of these drugs, but one interesting reaction has received relatively little attention: a number of patients with severe hypertensive disease treated with hexamethonium (with or without hydralazine) have developed an unexplained type of dyspnea with pulmonary changes likened to the Hamman-Rich syndrome.

This condition is characterized by a sudden onset of dyspnea, cyanosis, fever, cough, and chest pain; it may progress to death in one month. There is no certain knowledge of the cause of this reaction, but the lesions are thought to be the result either of attacks of left ventricular failure modified by intermittent hypotension or of a pulmonary collagen disease. Pathologically there is acute diffuse interstitial pulmonary fibrosis which is identical with the changes present in patients having the Hamman-Rich syndrome and which resembles pulmonary scleroderma.[23, 24]

Acetazolamide *(Diamox)*

Acetazolamide is a mild diuretic which is frequently given to cardiac patients in order to decrease their requirements for the more potent mercurial diuretics. It is an inhibitor of carbonic anhydrase which normally makes hydrogen ions available for exchange with sodium ions in the glomerular filtrate and for the formation of ammonium ions from ammonia by the renal tubular cells. It is well known that patients receiving acetazolamide with ammonium chloride may develop severe acidosis because of their inability to excrete the excess chloride ion. There is evidence that patients with severe congestive heart failure and chronic congestion of the liver are apt to develop ammonia intoxication spontaneously, and both ammonium chloride and acetazolamide have been implicated as etiologic factors in the precipitation of hepatic coma in patients with severe congestion of the liver caused by cardiac decompensation.[25]

Chlorpromazine *(Thorazine)*

The phenothiazine tranquilizers, which include chlorpromazine (Thorazine), promazine (Sparine) and prochlorperazine (Compazine), have so many pharmacologic actions that it is surprising that they do not cause more undesired side effects than they do. Pertinent to our present discussion is the fact that these drugs quite frequently cause an extrapyramidal syndrome which is similar to, if not identical with, Parkinsonism with generalized cogwheeling, rigidity, tremor, pill-rolling motion of the fingers, mask facies, skin changes, attitude of flexion, gait disturbances, drooling, and poverty of movement. Such reactions occur occasionally when the drugs are used in modest dosage, and the incidence approaches 50 per cent when high dosages are employed. The symptoms subside rather slowly after the drug is stopped, and they may persist for two or three months.[26]

By now everyone knows that chlorpromazine can cause jaundice, but the erroneous notion is prevalent that this jaundice is invariably benign and of an obstructive nature. We now know that hepatocellular damage is not infrequent,[27] and that rather severe jaundice has been reported to follow a single relatively small dose of the drug.[28] Indeed, there is good evidence that chlorpromazine can cause clinical hepatitis in the absence of icterus (anicteric hepatitis).[29]

Cycloserine

One of the newer antibiotics which shows promise of being helpful in treatment of patients with intractable tuberculosis is cycloserine. Dosage of this drug has to be regulated carefully, as slightly more than the minimal effective dose precipitates grand mal seizures in a high percentage of patients. Electroencephalograms have not been helpful in predicting which patients can be expected to have epileptiform seizures. In addition to the "epilepsy," neurotic, psychotic, and personality changes have been reported. The drug is especially dangerous for patients who have diminished kidney function because it is excreted by the kidneys, and renal damage leads to its retention in toxic amounts.[30]

Antibiotics

Various antibiotics have been responsible not only for control of numerous serious infections but for the whole spectrum of garden variety drug reactions. In line with our present discussion, one is outstanding. Pseudomembranous enterocolitis has been a recognized entity for many years, cases of which have been reported in the literature from time to time, but, with the advent of antibiotic therapy—specifically therapy with agents which destroy the normal intestinal flora—there have been numerous instances of the appearance of this malignant condition. It is impossible to estimate how many patients have lost their lives as the result of a disease which is essentially iatrogenic.[31, 32]

Isoniazid

One of the most important agents used in the treatment of tuberculosis is isoniazid. Shortly after it was introduced there were reports of euphoria and psychotic reactions, but it now appears that the euphoria is directly related to the actual clinical improvement of the patient, and psychotic reactions do not occur in a discernible cause and effect relationship with the drug. However, one complication of importance has been reported, namely a fairly typical peripheral neuropathy. This complication evidently bears a relationship to the dosage of the drug employed and apparently affects adults exclusively. Symptoms are paresthesias, numbness, burning pain, weakness, etc., and signs include hypesthesia and exaggerated or absent deep tendon reflexes. This neuropathy resembles the natural and experimental neuritis which is caused by pyridoxine deficiency, and the consensus now is that isoniazid functions as an antimetabolite against pyridoxine. The early neuritis does indeed respond to pyridoxine therapy, but if it is permitted to progress it tends to become permanent.[33]

Iron

Our attention has understandably been directed toward the newer therapeutic agents, but some of the old standbys must also be held responsible for

iatrogenic syndromes. Everyone is cognizant of the minor gastrointestinal disturbances that so frequently accompany iron therapy and of the severe, fatal reactions that result from acute overdosage of iron salts. Chronic toxicity must not actually be a great hazard or we should have heard more of it, but one cannot afford to forget that hemachromatosis, or a similar entity, is associated with increased iron absorption. This is probably at times more than a simple hemosiderosis, and it must be considered when one embarks upon the long-term treatment of patients with "refractory" anemia.

Conclusion

"Man is a prober and meddler, and in this, so long as he holds true to his own gifts, he will not stop."[34] Perhaps "a little knowledge is a dangerous thing" but "very few of those who have followed the history of medicine, from the first trepanning operation to the modern transplantation of the cornea, would agree that we should have abandoned medicine because at each stage in its history first attempts at operations have been unsuccessful. A little learning, if it is the first learning, is the way in which men move on to new knowledge, and it can be regarded as dangerous only when the practitioner or patient overestimates it. . . . Learning is not dangerous because there is only a little of it, but it is dangerous not to know just how little there is."[35]

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If there is one thing which I have learned as a result of four years at the United Nations it is that the sense of justice is very much the same in every man. Regardless of whether he comes from Asia, Africa, Europe or America, he has very much the same idea of fair play as his fellow man who may come from a country 10,000 miles away. . . . The future of the world depends on the extent to which we can base international relations on that sense of justice and fair play which is in every human heart.

—Henry Cabot Lodge

Ataractics

A Study of the Current Status of Tranquilizing Drugs

PAUL E. FELDMAN, M.D., *Topeka*

My opening remarks might be considered as "signs of our time," as, for instance, a chain drugstore advertisement which read:

Relax with Tranquil
SALE
Tranquilizing Tablets
NO PRESCRIPTION NEEDED

Or perhaps you may have seen in the February 1957 issue of *Better Homes and Gardens* in the department entitled "Your Pet and Mine," edited by Veterinarian Wayne H. Riser, a problem sent in by a subscriber who stated: "My dog becomes afraid and very excited during a thunderstorm. Is there a drug that he could be given to calm him?" Answer by Dr. Riser: "Many drugs have been tried for this fear of storms. Until recently, none has been successful. However, the new drug Thorazine has been reported to give good results. Discuss this with your veterinarian and ask him what his results with the drug have been."

In our general hospitals Thorazine and other tranquilizers are now routinely prescribed preoperatively to allay operating room anxiety. Spirits of ammonia are being replaced in our funeral parlors by Miltown.

A recent "Grin and Bear It" cartoon depicts a harassed school teacher sitting at her desk in front of a rowdy class with a bottle of pills on her desk and the school principal saying to her, "Tranquilizing pills have no place in the teaching profession, Miss Figby! Next, you'll be taking a drink."

From bits of information like this we begin to realize how commonplace these drugs have become—how much they are now a new and vital characteristic of our type of society.

It is reported that women get together for an afternoon of bridge or tea and the hostess passes around a bottle of Miltown. At some of these affairs tranquilizing tablets are passed out by the handful. If you can't get them on prescription, there is an ample black market where you can buy them at a considerably marked up price.

The old time needle-beer parties and the more recent marihuana parties are being replaced by mescaline or lysergic acid diethylamide parties. The participants ingest some type of hallucinogen and, when they wish to terminate the experience, they use a blocking agent which is usually one of the new tranquilizing drugs.

In many ways, all sorts of people are taking these drugs for "kicks," and the drugs have acquired the title of "happiness pills."

I don't believe that I am exaggerating the present situation. There are surveys, fantastic as they may seem, which indicate that millions and millions of tranquilizer tablets are being ingested daily. A medical survey last year indicated that from four to six of every 10 prescriptions were being written for some form of tranquilizer.

If this is true, and I don't doubt it for one minute—if proper, accepted medical practice is based upon what the majority of the profession do, then I have to conclude that the promiscuous prescribing of tranquilizers is a proper and ethical practice.

The development of tranquilizers has made possible a new and effective treatment regime in many mental hospitals and has helped increase discharge rates. It has awakened public interest in problems of mental health. However, the indiscriminate use of tranquilizers is fraught with many dangers, some of which are outlined here.

It is true that all of us do not see eye-to-eye about the efficacy of these drugs, and there is a substantial number of sincere opponents to this practice. There are many ethical, competent psychiatrists and general practitioners who never prescribe tranquilizers, yet appear successful in their management of emotional and nervous disturbances.

The entire field of tranquilizers and tranquility has been considered under the term "ataraxis." Fabing of Cincinnati who introduced the term, borrowed it from the Greek word "ataraxia" which means "freedom from disturbance of mind and passion." Some anonymous wit has defined ataractic drugs as "don't give a damn pills."

Psychopharmacotherapy—the treatment of mental illness with drugs—is probably as old as medicine itself; but in a more limited sense, ataraxic therapy was ushered in about the time of World War II with the development of narcoanalysis. The effects

Presented before a regional meeting of the American College of Physicians, Topeka, March 15, 1957. Dr. Feldman is director of research and education, Topeka State Hospital.

of intravenous sodium amytol upon catatonia and the general effects of abreaction upon mental symptoms stimulated investigators to look for new and more effective drugs which might be used in the treatment of mental disease.

One of the first new drugs to appear was mephenesin which was marketed by Squibb under the trade name of Tolserol. During the period that this drug was tested experimentally, it was found to be effective in the treatment of everything from delirium tremens to senile dementia. And then, as often happens with an experimental drug, the charm wore off and it was found to be about as effective as tap water for these same states. Even today though, it still has slight merit as a muscle relaxant, provided you use adequate dosage.

In fact, this particular property of mephenesin, its muscle relaxant property, stimulated investigators to look for a drug which had a more prolonged mephenesin effect, and the result of this search culminated in what we today know as Miltown or Equanil. Miltown is a mephenesin-like drug with a more prolonged muscle relaxant effect.

Since the introduction of Tolserol, a number of newer products have appeared. Interest in rauwolfia led Ciba to market this alkaloid under the trade name of Serpasil, and soon other pharmaceutical houses followed suit using the generic name of reserpine.

At about the same time, investigators seeking a superior antihistaminic, attempted by starting with the mother-substance "Phenergan" to arrive at a product which had the antihistaminic properties of Phenergan without its toxic effects. Their search culminated in the development of Largactil which is chlorpromazine hydrochloride, which Smith, Kline and French patented in this country under the trade name of Thorazine.

In rapid succession have appeared Frenquel, Meratran, Ritalin, Sparine, Compazine, Suavitil, Atarax, Pacatal, Trifalon, Vesprin and a host of numbered, experimental products.

These drugs can be roughly divided into two groups: (1) the central nervous system stimulants as exemplified by Meratran and Ritalin and (2) the tranquilizers as exemplified by reserpine and Thorazine.

We are aware of a number of physiological differences between these drugs, but with minor exceptions our present state of ignorance does not permit us to ascribe any specificity to any of them as yet. Frenquel, for instance, is supposed, according to William S. Merrell Company, to be a specific for hallucinations and postoperative confusion, but there is ample scientific literature to refute this claim.

Meratran, Ritalin, and other central nervous system stimulants have been found by some investigators to be effective in the treatment of endogenous depressions. True as this may be, it is questionable whether it is a form of treatment for depression superior to some of our more firmly established therapies. Clinically there are more contraindications to the administration of amphetamine-like drugs than there are to electro-convulsive therapy.

In spite of the discrepancies in the literature, there are a few generalizations about ataraxic drugs which, all agree, do apply:

1. All of them do something, some more than others, but none are inert substances.

2. Their mode of operation and fate in the body are obscure. Pharmacological studies have shown that some drug is eliminated in the urine, some detoxified by the liver, and some deposited in the brain, but as yet we are unable to account for the major portion of the drug.

3. None of these drugs are completely non-toxic.

4. There is absolutely no evidence to indicate that these drugs alter basic personality patterns. They manifest their beneficial effects by diminishing tension, anxiety, and hyperactivity.

5. Therapeutic effectiveness is dependent upon individualizing the dosage. What may be an adequate dosage for one patient, may be completely inadequate for another, even though both patients might exhibit identical clinical symptoms.

6. Evidence appears to be overwhelming that these drugs are:

   a. Strikingly effective in relieving excitements, agitation, anxiety, and confusion.

   b. Apparently effective in alleviating hallucinations and delusions, especially in paranoid patients.

   c. Helpful in reducing hyperactivity in mental defectives, thus enhancing their performance.

   d. Helpful in relieving tremors and tensions of cerebral palsied children.

   e. More effective in hospitalized patients than in outpatients.

   f. Effective for the tension, apprehension, and tremor of the alcoholic.

   g. Reducing the use of prefrontal lobotomy and electro-convulsive therapy.

   h. Of uncertain value in the treatment of depression and have in many instances induced exacerbation of depression.

Individual claims of cures can be found in the literature, but most proponents as well as opponents of ataraxis feel that other than for improvement in certain symptomological aspects of mental illness, nothing more should be expected from these drugs. Most men who employ ataraxis use these drugs as only one aspect of a total treatment program.

Since these drugs then, at best, merely mask symp-

toms, unless some more effective therapeutic measure is employed concurrently, there is little likelihood that the underlying factors which caused symptoms will be altered, and these drugs will have to be administered indefinitely. Upon their discontinuance there will usually be a recurrence or exacerbation of symptoms. This is being borne out by the two-, three-, and four-year follow-up studies which are beginning to appear in the literature.

In our own studies, two-thirds of the patients who have been released on tranquilizer therapy are still taking medication. Of the remaining third, most, after stopping medication, have found their way back into the hospital. In long term treatment, the maintenance dosage is substantially below the original therapeutic level, but complete cessation of medication leads to an exacerbation of symptoms.

One of the major drawbacks to tranquilizer therapy is the untoward harmful effects produced by them. None are completely harmless, not even Miltown which is popularly thought to be completely non-toxic. There are numerous reports of addiction or convulsions with this supposedly harmless drug.

The major complications of ataraxis are those associated with blood changes, hepatic dysfunction, the development of a convulsive diathesis, the results of inadequate dosage during the incipient phase of a major psychotic state, the development of depression, and failure of the air-passageway defenses.

To date there have been approximately 50 cases of agranulocytic angina reported in the literature. Of these, about 10 to 15 per cent have terminated fatally in spite of heroic measures. Various investigators quote an incidence rate of from 1:1,500 to 1:15,000. It is my personal conviction that if all cases of agranulocytosis, fatal and non-fatal, were reported, we would find an incidence of about 1:300.

The potential development of this dreaded complication must be kept in mind at all times, and it is one of the major reasons for considering ataraxic therapy a serious medical procedure which at all times must be under the supervision of a physician. If you rely upon the usual monthly blood studies to forewarn you of an impending agranulocytosis, it will only lead to disaster. It is far better to place your reliance upon your clinical estimate of the patient and if one or more of the triad of symptoms appear [(1) fever of undetermined origin, (2) sore throat or (3) lesions of mucous membranes] discontinue medication at once and treat as an agranulocytosis until proven otherwise.

The usual disturbances of hepatic function are those associated with intrahepatic biliary obstruction. It may occur in about 1 per cent of patients, and there is division of opinion as to how it should be managed. When jaundice appears, some discontinue medication, others do not, and all seem to have about equal success in the management of this complication.

Most reports suggest that jaundice occurs within the first 30 to 60 days of medication and that it is not related to dosage size, but is more in the nature of an allergic response or a Herxheimer reaction. Another theory suggests that as a result of intestinal hypomobility, there may be blockage at the cholechoduodenal sphincter with consequent biliary stasis and intrahepatic obstruction.

There are reports of cases of jaundice which have occurred many months after tranquilizer therapy was started, but in every case I have been able to follow I have found that medication had been interrupted and that jaundice appeared 30 to 60 days after medication was reinstituted.

Clinically you might have great difficulty distinguishing between Thorazine jaundice, an infectious hepatitis, or a gallstone syndrome. I have seen autopsies upon patients who had at some previous time had Thorazine jaundice, and gallstones were demonstrated.

Another hepatic complication of tranquilizer therapy is just becoming apparent as a result of multiple-year follow-up studies in which a high incidence of pathological obesity and fatty degeneration of the liver is being reported. We are also becoming aware of non-icteric hepatitis associated with pain in the upper right abdominal quadrant. Recently there have been reports of pain in the lower right abdominal quadrant, due to muscle spasticity and closely resembling acute appendicitis.

If a patient without a previous history of seizures should develop convulsions during the course of tranquilizer therapy, such an occurrence must be regarded as a major complication. The unexpected appearance of convulsions indicates a serious disturbance of brain function and metabolism. Should seizures develop, they must be assessed in the light of the psychiatric gain made as a result of therapy; if it is felt that the improvement in symptomatology warrants it, seizures can be quite successfully controlled by the use of some anti-convulsant such as Dilantin.

Some of the drugs, notably the reserpine products, are known to produce depressions of serious magnitude. The appearance of suicidal trends is a major complication of therapy.

The administration of an inadequate dosage of drug during the incipient phase of a major psychosis may permit a full blown psychosis to appear which might have been avoided or ameliorated by more adequate measures. I do not mean to imply that all mental disturbances, regardless of severity, should

be referred to the psychiatrist. There are too few to go around, and in addition minor neuroses and other related emotional disturbances rightfully belong in the domain of the practitioner. I only remind you that sometimes the incipient phase of a major break may be ushered in by what may appear as minor symptoms. It is at this phase of the illness that the most good can be done therapeutically with proper measures.

I cannot help but be impressed by the number of acutely and severely psychotic patients who are finding their way into our mental hospitals. They reach hospitals late as far as the optimal time for appropriate treatment is concerned, and we obtain a history of their having been treated with 10 or 25 mg. of Thorazine per day for long periods of time.

I would like to mention one additional major complication, the nature of which as yet is obscure. Some investigators are reporting a high incidence of pneumonitis during tranquilizer therapy, and recently there have been reports of deaths which were due to aspiration strangulation. In these cases there appears to have been a catastrophic failure of the air-passageway defenses to respond to the presence of foreign material in the trachea.

There seems to be an almost infinite variety of minor untoward effects of tranquilizer therapy, a few of which are:

Drowsiness

Dizziness

Parkinsonism and a variety of extrapyramidal symptoms

Allergic phenomena

Disturbances of vision

Corneal ulcerations

Potentiating action on sedatives, hypnotics, and narcotics

Hypotensive responses, especially orthostatic type

Gastrointestinal disorders including reactivation of previously dormant ulcers

Increased incidence of infectious processes.

These minor side reactions may occur in a variety of combinations and are more marked and frequent with some drugs than with others. Every one of the minor side reactions listed can be managed by (1) administration of proper antagonistic medication, (2) lowering dosage of ataraxic drug, or (3) discontinuation or change of medication.

Perhaps one of the most significant advances in ataraxic therapy during the past year has been the development of an appreciation that these untoward effects are inevitable and perhaps not necessarily undesirable or detrimental, also, that these patients can be kept comfortable and active by the suitable management of side reactions.

Fabing, who coined the term ataraxis, has facetiously fantasied that "an enemy may drop a ton of ataractic drug into the water supply of our major cities and then march triumphantly though our streets while we sit in a rocking chair at the window, not lifting a finger in our defense because we are too listless and inwardly peaceful to get up on our feet and fight for our freedom."

There are also some good effects of the tranquilizers which even the opponents of ataraxis agree upon. The development of tranquilizer drugs has been a shot-in-the-arm for psychiatry in general. It has awakened tremendous public interest in problems of mental health, our state hospitals, and related agencies. It has stimulated research, not only in the field of ataraxis but in related fields as well. It has hastened the investigation of the experimental psychosis and the role of serotonin in mental health and in disease.

In some of our state hospitals where inadequate staffing prevented a modern therapeutic program, it has made possible a treatment regime to which thousands and thousands of patients have responded. In some areas of this country it has resulted in significant increases in discharge rates from state hospitals and in a substantial reduction in seclusion and restraint rates.

Within the past few weeks both the Food and Drug Administration and the New York Academy of Medicine have issued statements condemning the indiscriminate use of tranquilizers by both the layman and the medical profession.

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Topeka, Kansas

Wonder is the beginning of wisdom in learning from books as well as from nature. If you never ask yourself any questions about the meaning of a passage, you cannot expect the book to give you any insight you do not already possess.

—Mortimer Adler

Carcinoma of the Prostate

A Review of Symptoms, Diagnosis, and Prognosis

W. A. ROLL, M.D., ***Halstead***

When one is considering diseases which afflict the aged, carcinoma of the prostate stands high on the list. Incidence of carcinoma of the prostate is more frequent than that of any other cancer in the male, and this lead is likely to grow as the average age increases.

There are many studies to show increasing incidence with increasing age. Hudson found prostatic cancer in 13 per cent of men above 50 years of age subjected to perineal biopsy. Moore found at autopsy that 20 per cent of men over 40 years of age had prostatic malignancy. Only one cancer out of five was clinically manifest. These studies show the prevalence of this disease and indicate that it is a problem which deserves the attention of every practicing physician.

The etiology is as yet unknown. We know that eunuchs do not have cancer of the prostate. We infer from this that testosterone stimulation is necessary for malignancy to develop in the gland. However, we must remember that carcinoma develops when the estrogen-androgen balance is being tipped in favor of estrogen. It is at a time when atrophic changes are occurring in the prostate. Moore believes that most, if not all, carcinomas of the prostate originate from atrophic acini. This may explain why most carcinomas arise in the posterior lobe since this lobe shows more atrophy and never participates in hypertrophy as the other lobes may do.

Almost all malignancy originating in the prostate is adenocarcinoma. This varies from anaplastic to well differentiated growths which can be identified only by an expert pathologist. The diagnosis depends on the presence of anaplasia, loss of orientation, invasion of perineural lymphatics, and changes in staining properties. Figures 1 and 2 are examples of a well differentiated carcinoma and an anaplastic carcinoma. About three per cent of prostatic cancers are of the squamous cell variety.

The disease process apparently remains localized for prolonged periods of time, and at present we do not know how many latent carcinomas actually become clinically manifest. When spread occurs, it takes place by local extension and by both hematogenous and lymphogenous routes. The first distant spread is to the internal and external iliac lymph nodes. The bones of the pelvic girdle are also commonly involved with metastases. Seeding of the lumbar spine may well occur via the venous plexus of Batson.

The most common symptoms are those due to urinary obstruction such as urgency, frequency, and dysuria. These may be due to an associated prostatic hypertrophy. Hematuria also is a common finding and usually signifies invasion of the bladder or

Carcinoma of the prostate is the most common malignancy in men. Treatment by radical excision is curative if the diagnosis is made early enough. Estrogens may be used for palliative treatment.

Figure 1. Photomicrograph of well differentiated adenocarcinoma of the prostate.

From the Department of Urology, Hertzler Clinic and Hertzler Research Foundation, Halstead.

urethra by tumor. Initial symptoms can be due to the metastases and consist of any of a large variety of phenomena, depending on the organ affected. Backache, anemia, weight loss, and general malaise are among the more common ones.

Early carcinoma causes no symptoms whatsoever, and it is usually found during a routine examination. It is first detected as a firm or hard nodule in the posterior or lateral lobes of the prostate. Later, as the cancer grows, the entire gland becomes fixed to the surrounding tissues and typically feels stony hard and nodular. The bones may be affected by either osteoblastic or osteolytic types of metastases. The acid phosphatase will be elevated in 80 per cent of cases with bony involvement.

Diagnosis of far advanced cases usually is easy; however, in early or questionable cases a biopsy must be obtained. This is particularly important when the disease is apparently confined to the prostate. Every nodule found in the prostate should be considered malignant until proved otherwise. The series reported by Jewett and that by Kimbrough show that 50 per cent of solitary prostatic nodules are malignant. We have found this to be true in our own series of patients.

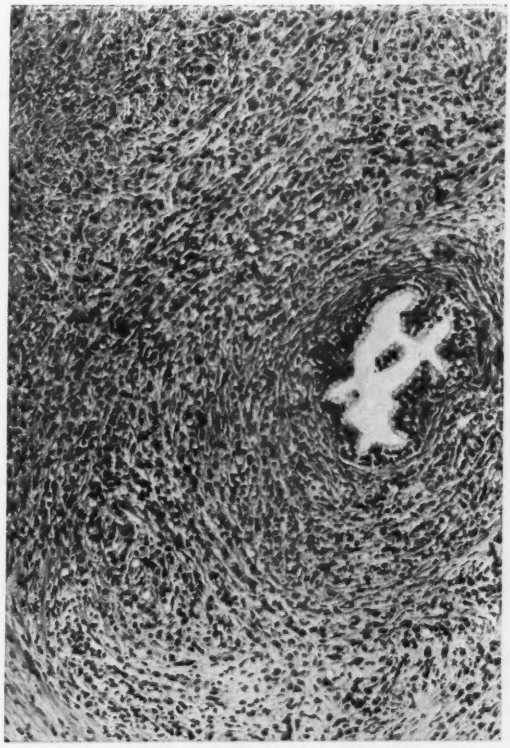

Figure 2. Photomicrograph of anaplastic carcinoma of the prostate.

The biopsy can be obtained either by transperineal or transrectal exposure. Some men have had success with a needle biopsy, but it is difficult when only a small nodule is present and is reliable only when positive. The transurethral method of biopsy is not satisfactory in early malignancies because the tumor arises in the periphery of the gland and tissue may not be obtained from it.

Various other tests can be performed such as the determination of the acid phosphatase content of the prostatic secretion or examination of the secretion for malignant cells. Still other tests on the blood and urine are being developed but are not yet reliable. We must still depend on microscopic examination of the tissue.

Treatment is either curative or palliative and depends upon the state of the disease when first found. The only method of cure is radical and complete excision of the tumor, possible only when the disease is localized in the prostate. Approximately five per cent of cases now seen are curable; however, Kimbrough reports that 50 per cent of cases seen by him are operable. Jewett states that 11 per cent of his cases are operable. Certainly more patients will be saved as the disease is recognized in its early stages.

Radical excision can be performed by either the perineal or the retropubic route. We use the perineal route and do our biopsy, frozen section, and radical removal at the same time. Others prefer the retropubic approach, either because of training or because of a lack of frozen section facilities. The route of excision is relatively unimportant, but the time of excision is important. Mortality and morbidity are small in either procedure. Almost all patients are made impotent, but only about five per cent are left incontinent.

Palliative treatment is aimed at the relief of symptoms and at the slowing or stopping of tumor growth. The first objective is usually the relief of urinary obstruction, most easily accomplished by transurethral resection of obstructing tissue. The tumor can then be caused to regress by castration or by administration of estrogens.

Regression will occur in about 80 per cent of cases treated and will last a variable length of time. Several studies have been performed which indicate that combined therapy with castration and the administration of estrogens gives best results. We prefer this approach and give 1 mg. of stilbestrol daily after castration. If the patient will not permit castration, we give 5 mg. of stilbestrol daily. Others prefer to give Tace as the estrogen since adrenal hypertrophy does not occur with its use as it does with stilbestrol.

After the tumor begins to grow again, treatment is difficult, and no satisfactory answer has been

found. Some are injecting radioactive material into the local growth and are obtaining fair results. Others are giving radioactive phosphorus in an attempt to destroy bony metastases. Adrenalectomy by surgical excision or by medically induced atrophy is also being tried. Most patients obtain considerable relief from their symptoms with the administration of corticosteroids. This relief is temporary, and a regression of the tumor is seldom seen.

Radical excision of the early carcinoma gives the best prognosis by far. Jewett reports a ten-year survival of 50 per cent when the tumor is microscopically confined to the prostate. This compares exceptionally well with the ten-year survival of 53 per cent for normal men in that age group. Thirty-seven per cent of the patients in whom the tumor was confined to the prostate as evidenced by rectal palpation, lived ten years.

The prognosis in patients in whom the tumor cannot be removed depends upon the degree of malignancy and the presence or absence of metastases. The combination of castration and estrogen gives the best possible results, as reported by Nesbit and Baum in their series and more recently by Ganem in his series. The former report a five-year survival of 44 per cent when no metastases are present and 21 per cent when metastases are present. Castration alone gives a survival of 31 per cent when no metastases are present and 20 per cent when they are present. Estrogens alone give a poorer result.

Until a chemical cure is discovered, our greatest hope for better control of this disease depends upon earlier diagnosis and treatment. Earlier diagnosis depends upon routine rectal examinations and biopsy of all prostatic nodules. Removal of the entire prostate when the tumor is still confined will give a ten-year survival rate which is practically normal.

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It is the great destiny of human science, not to ease man's labors or prolong his life, noble as those ends may be, nor to serve the ends of power, but to enable man to walk upright without fear in a world which he at length will understand and which is his home.

—*Paul B. Sears*

Acute Intermittent Porphyria

Report of a Case Treated with Chlorpromazine

JOHN E. SWEENEY, M.D., ***Topeka***

Acute intermittent porphyria is a disease of unknown physiologic pathology. The characteristic metabolic defect is the production of certain abnormal porphyrin products and their excretion in the urine. Associated with this may be one or more of a classic triad of signs and symptoms; severe abdominal pains and constipation, peripheral neuropathy, and various emotional disturbances. A number of recent reviews summarize the clinical aspects of the disease.[1-4] Despite intensive study, the nature of the basic metabolic defect is not clear, its relation to the symptoms observed is unknown, and the mechanism by which symptoms are produced has not been demonstrated. Therefore, no truly specific treatment is available, and until recently there has been no satisfactory way of handling these patients, who are often desperately ill and may die of the disease.

One such patient has been under observation for the last two years, and has been found to respond symptomatically in a specific fashion to chlorpromazine, though there has been no observable change in the metabolic disturbance. Severe abdominal pain and gastrointestinal disturbances have been consistently relieved and psychic disturbances improved whenever this drug has been used. At the time this patient was being studied, similar results were being noted by others, and have since been reported.

The use of chlorpromazine in acute intermittent porphyria rests primarily on an empirical basis, and probably this is not specific treatment as far as the basic disorder is concerned. Nonetheless, it provides dramatic, consistent, and effective relief of symptoms and frequently leads to remission. This alone makes it the most satisfactory agent available at present.

Case Report

The patient is a forty-eight-year-old, married, white female first seen on January 27, 1955, complaining of severe abdominal pain, nausea, generalized aching and urinary frequency. She gave a history of rheumatism during childhood, and of repeated episodes of pain in the back and abdomen with nausea. At eight years of age, she had an appendectomy with relief of these symptoms. She had no difficulty with her four pregnancies, but shortly after the last child was born in 1935, she began to have episodes of upper abdominal pain. After a cholecystectomy in 1940 complicated by an abscess, she still had pain, and in 1942 a hysterectomy was done followed by some improvement. In 1951, she was found to have diabetes mellitus. This was managed by diet alone, and she got along reasonably well, though in 1953 she had a period of weakness and depression. She had been habitually constipated, and used cathartics frequently. She had had other episodes of depression in the past, and gave a history of fairly frequent urinary infections. Her father had diabetes, but little information is available about the rest of her family. The urine of one child has been tested for porphobilinogen with negative results.

When the patient was first seen, she had been depressed and irritable for three months, she had been "worse" for four or five weeks and "down in bed" for five or six days. Abdominal pain had persisted despite "shots" by her family physician. On examination, she did not appear to be having as much pain as she complained of. She was apathetic and depressed, and quite uncommunicative. The abdominal wall showed multiple old scars, but no hernia. Although the patient complained of severe abdominal pain, there was no spasm and the wall was flaccid. No masses were palpable. On pelvic examination, there was tenderness about the bladder. Neurological examination was normal. She was afebrile. The blood pressure was 120/65. There was some evidence of dehydration. The physical examination was otherwise not remarkable.

Laboratory findings showed pyuria and acetonuria, and an electrocardiogram compatible with electrolyte disturbance. The patient was treated with penicillin and streptomycin for the infection, dimenhydrinate, parenterally, and chlorpromazine, 25 mgm. four times a day by mouth, for the abdominal symptoms, and gradually improved with return of laboratory tests to normal. She remained quite depressed, and was seen by a psychiatric consultant who recommended a trial of Dexamyl®. She was discharged on this medication only.

Within three days, she began to have nausea and

abdominal pain, and was readmitted to the hospital with essentially the same picture, complaining of pain for which no organic basis could be found. The diabetes was controlled by diet alone as her symptoms subsided, and transient acetonuria was felt to be due to starvation. During her stay, the patient was treated with antibiotics, meperidine, dimenhydrinate, and chlorpromazine, and once more gradually improved. Cystoscopy showed a membranous trigonitis. She was again discharged on Dexamyl® and an antibiotic.

Four days later, she began to have pain again, and was finally readmitted in a similar state of semi-starvation and dehydration with a mild urinary infection. Once again she was treated with meperidine, chlorpromazine, and erythromycin. This time on discharge she was instructed to take chlorpromazine, 25 mgm. four times a day, as well as Dexamyl®.

On this regimen she appeared to do better and showed steady improvement for two months until she stopped the medications of her own accord. Within five or six days, she began to notice tiredness, recurrence of abdominal pain, loss of appetite and nausea. On June 2, she was readmitted with the same picture but without significant urinary difficulties. Chlorpromazine was started promptly and her symptoms cleared within three days. Three times in the next five months, she discontinued medications and experienced recurrence of symptoms.

It was in this period that she first reported that some of her urine specimens were "inky black" in color. Her urine was noted to darken in sunlight. The urine gave a negative test for homogentisic acid and coproporphyrin, but a positive reaction for urobilinogen in a dilution of 1:40, and a positive test for uroporphyrin after acidification. It was at this time that the diagnosis of the underlying disease was established.

Aside from intermittent glycosuria and acetonuria during her acute symptomatic episodes, laboratory studies have been unremarkable. Blood counts have always been normal. The highest sedimentation rate was 26 mm./hour. Most blood chemistries have been normal. Fasting blood sugars without insulin have ranged from 125 to 185 mgm. per cent. The glucose tolerance curve is moderately elevated. X-rays of the spine, upper gastrointestinal series, intravenous and retrograde pyelograms have been normal.

Once the diagnosis of porphyria was established Dexamyl® was discontinued because of its barbiturate content (though this did not appear to have any direct effect in producing symptoms). Chlorpromazine was continued because it had demonstrated a beneficial effect on her symptoms. This effect has since been shown to be highly specific. On repeated occasions the patient has discontinued chlorpromazine because she was "feeling well." For the next forty-eight hours, she seems to be more active and alert and then becomes depressed, "tired," and very irritable. She notes the passage of dark urine, experiences cold chills and sweats about the fifth day, and then begins to have severe abdominal pains and nausea, and refuses food. On one occasion sweating predominated on the right half of the body.

In February, 1957, she was admitted to the hospital for regulation of her diabetes, and at that time chlorpromazine was deliberately withheld and the patient observed. This same sequence of events took place, and when she began to have abdominal pains chlorpromazine was again started in a dose of 25 mgm. four times a day, orally, with relief of symptoms in less than six hours. During this time, considerable quantities of porphobilinogen were continuously excreted in the urine, and specimens taken both during the period of withdrawal and after treatment was resumed were positive for this substance in dilutions of 1:320 to 1:640. So long as she takes 25 mgm. of chlorpromazine two to four times a day she gets along well.

Coulonjou, et al.[5] reported a case of acute intermittent porphyria, treated with chlorpromazine in 1953, and one treated in 1954 in India has been reported by Singh and Chandy.[6] This latter patient was given chlorpromazine as a hypotensive agent and the author attributed the improvement in her overall picture to the concomitant use of ACTH. However, ACTH has been very inconsistent in producing remissions in this disease and generally only slowly. Muller[7] reported a remission after a "lytic cocktail," which included chlorpromazine. In this country, Durst and Krembs[8] mentioned relief in one case treated in 1955. Melby, Street and Watson[9] have published reports of nine cases, either treated by them or reported to them, which have shown this same specific benefit from chlorpromazine, and Monaco, Leeper, Robbins and Calvy[10] have reported four similar cases. Martin and Heck[4] mention the use of chlorpromazine without giving any specific details or citing cases.

The benefit from the use of this drug in all of these cases has been consistent, regular and reproducible. When given in adequate dosage, prompt relief of pain, vomiting and major emotional disturbances is to be expected. Apparently, a slower remission of acute neurological disturbances has been noted,[11] though established paralysis is not altered. Some patients after being treated during the acute phase will enter a remission and require no treatment until the next attack. Others, like the patient reported here and Melby's[9] Case 7, require continuous treatment to prevent recurrence of symptoms. No case has

been reported that did not show at least marked improvement.

No consistent effect on the excretion of porphyrins has been noted, though in cases where remission follows the levels may fall. Monaco, et al.,[10] have made the interesting observation that when chlorpromazine is given to patients with latent porphyria, manifested only by the urinary products, an excessive and disproportionate somnolence is induced. In the case reported here the amounts of porphobilinogen have shown little variation though as symptoms improve pigmented materials disappear. The drug has been given both intramuscularly and orally, and doses have varied from 50 mg. a day to several hundred in reported cases. Generally, 100 mg. given parenterally will control acute symptoms, and patients thereafter can be treated with oral medication usually in the dose of 100 mg. a day or less.

One can only speculate on the mechanism of action of chlorpromazine in these cases. One attractive hypothesis is that this drug's recognized tranquilizing effect corrects emotional disturbances which might precipitate the acute attacks. It is well known that these patients have many personality peculiarities, and are notoriously unstable. A number of authors have commented on this, and both Gunther[12] and Roth[13] have postulated in the past that emotional difficulties may well precipitate the symptoms in a person who would otherwise have only the latent metabolic defect (presumably inherited). This hypothesis would certainly be consistent with the events in the case here reported since the drug was used initially for the purpose of treating emotional difficulty, and apparently demonstrated its effectiveness in this respect, even before the diagnosis of porphyria was established.

A second hypothesis is that the drug in some way interferes with autonomic pathways which are involved in the production of the symptoms. Ganglionic blocking agents have been demonstrated to be of benefit in the abdominal crises, and chlorpromazine is thought to have an effect both on the diencephalic autonomic centers, and also on the acetylcholine transmission system. This would appear to explain benefit noted in abdominal cases, but does not clarify the effect on the neurologic disturbances.

A third possibility is that chlorpromazine alters the actual porphyrin metabolism. This is known to involve certain oxidative enzyme systems, and chlorpromazine may depress these in some way. However, none of the metabolic data reported to date have demonstrated any alteration in the porphyrin metabolism that might go with this.

So far as the effect of other similar drugs is concerned, little is known as yet. Melby, et al.[9] noted two patients who were treated with reserpine and apparently had some improvement, but certainly not the dramatic and fairly complete relief of symptoms noted with chlorpromazine. This may be due to the slow action of this drug. They also reported one patient who had been treated with meprobamate, with no relief and possibly an exacerbation of symptoms. The effects of barbiturates in this disease are well known, and they are considered to be definitely contraindicated. Likewise, in some reported cases, the newer soporifics and sedatives have appeared possibly to precipitate attacks. It is worth noting that this patient was given dimenhydrinate intramuscularly at the beginning of each of her admissions and this seemed to be of some benefit.

Patients with the disease are sufficiently uncommon, and new drugs are so numerous that it may well be some time before the whole field can be adequately explored, particularly since great caution must be used to avoid precipitating attacks. In fact, Donnadieu, et al.[14] have reported the appearance of porphyrinuria in two psychotic patients treated with chlorpromazine. There are, however, insufficient data given to evaluate this observation and it has not been reported elsewhere to my knowledge.

The occurrence of diabetes mellitus in this case would seem to be coincidental except perhaps for a parallel hereditary factor. Sterling, et al.[15] reported three cases, in all of whom diabetes preceded the appearance of symptoms of porphyria, and Brunsting[16] mentions several cases of diabetes (or diabetic parents) in a series of "mixed" or cutanea tarda type (which may be a different disease). Generally, the incidence of diabetes as an "associated disease" does not appear to be excessive, nor does porphyria seem to be unusually frequent in cases of diabetes mellitus.

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PRESIDENT'S PAGE

DEAR DOCTOR:

Shortage of nurses is universal, a vexing problem of growing seriousness, threatening to become increasingly acute.

There are various reasons. Actually there is an increased proportion of active graduate nurses, 32 per 100 patients, as against 15 in 1930. But the work week is reduced by 23 per cent. There is less utilization of student nurses in training, and there are now only two-thirds as many nursing schools as in 1930. There is increased demand on a nurse's time for records and clerical work and for administrative duties. There is increased hospital utilization by more patients with a more rapid turn-over. More nurses are entering fields other than hospital nursing. Finally, an enormous factor, the number employed by federal agencies has increased seven-fold since 1930, from 4,703 to 31,164.

The trend is toward higher and higher standards of nursing education, increased stress toward training for administrative and supervisory capacity, and away from bedside nursing. Less and less is the graduate nurse prepared for, or interested in, direct patient care, "bedside nursing." Those services are very inadequately supplied by nurse aids and, to a very limited extent, by one-year-trained "practical nurses." The net result is inadequate nursing care of depreciated quality.

The military services have contributed largely to this situation. The registered nurse is granted a commission on the same basis as a West Point graduate and placed in line for promotion. These nurse-officers perform little or no "bedside nursing" and are essentially restricted to desk positions.

The graduate nurse, the R.N., does fill a particular need. She may very well continue with the higher educational requirements, including even the college degree if deemed necessary. The practical nurse is useful, but her capacity is definitely limited, and a great void exists between her potentialities and those of the R.N.

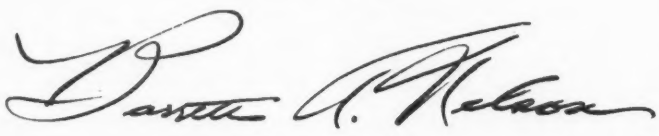
There is a simple answer to satisfy the crying need in this area. The need is for "bedside nurses." A two-year course of training in nursing schools re-established in hospitals throughout Kansas will effectively supply such nurses in ample quantity. The instruction must, of course, be both didactic and clinical, but any number of our hospitals can, as they have in the past, furnish very adequate instruction of this nature. There are large numbers of intelligent, alert, eager Kansas girls who earnestly desire to become nurses, but who cannot afford the tuition and other costs of present courses of nurse training.

Such "bedside nurses" would not qualify for the R.N. degree. They would not be considered as trained for administrative positions nor as supervisors. They would not be in line for military commissions, though they could probably be considered for non-commissioned officers.

They would, however, furnish a pool of competent, capable "bedside nurses" whose ambition and aim would be nursing care of the patient.

The medical profession can render a great service by cooperating with the nursing associations and the hospital organizations in a concerted effort to institute nursing schools of this type, and to obtain legislation to legalize the licensing of "bedside nurses" with such training.

Fraternally yours,



President

EDITORIAL COMMENT

A Modern Medical School

The following statement of the functions and structure of a modern medical school, approved by the House of Delegates of the American Medical Association on June 5, 1957, was prepared in collaboration with the Association of American Medical Colleges and represents the general concepts of that organization as well as the Council on Medical Education and Hospitals of the American Medical Association. Experience indicates that high standards are best nurtured in an environment in which there is not excessive concern with standardization. The concepts expressed here will serve as general but not specific criteria in the medical school accreditation program. However, it is urged that this document not be interpreted as an obstacle to soundly conceived experimentation in medical education.

Responsibilities and Objectives

As an institution of higher education, a medical school has three inherent responsibilities which are so closely related as to be inseparable.

1. A medical school should provide for its undergraduate students the opportunity to acquire a sound, basic education in medicine and should foster the development of lifelong habits of scholarship.

2. A medical school should contribute to the advancement of knowledge through research.

3. A medical school should contribute to the development of teachers, investigators and practitioners through programs of graduate education including residency training.

By virtue of its university orientation or as a result of the clinical facilities and personnel available, a medical school should assume additional responsibilities such as those listed below to the degree that its resources permit without weakening its basic program:

1. Leadership in the development of adequate opportunities for the continuing education of practicing physicians.

2. Professional service to patients primarily to fulfill its educational and research obligations.

3. Participation in the educational programs of other professions in the health field, such as dentistry, nursing, and pharmacy, as well as in selected areas of the general university program.

4. Training of technical personnel in paramedical fields.

A medical school should develop a clear definition of its total objectives, appropriate to the needs of the community it is designed to serve and the resources at its disposal. When objectives are clearly defined, they should be made familiar to faculty and students alike, so that efforts of all will be directed toward their achievement.

A statement of "The Objectives of Undergraduate Medical Education" has been prepared by the Association of American Medical Colleges. It is believed that this can well serve as the basis for a definition of this portion of the over-all objectives of a medical school and is reproduced in part below. The full statement can be found in the *Journal of Medical Education* (28:57-59 (March) 1953).

"Undergraduate medical education must provide a solid foundation for the future physician's development. It should not aim at presenting the complete, detailed, systematic body of knowledge concerning each and every medical and related discipline. Rather, it must provide the setting in which the student can learn fundamental principles applicable to the whole body of medical knowledge, establish habits of reasoned and critical judgment of evidence and experience, and develop an ability to use these principles and judgments wisely in solving problems of health and disease.

"Undergraduate medical education cannot achieve these aims if the student is relegated to a passive role. It must provide incentive for active learning on the part of the student. This can best be done by giving him definite responsibility in real, day-to-day problems of health and disease. This responsibility must, of course, be carefully graded to the student's ability and experience and must be exercised under careful guidance by the faculty.

"Given incentive to learn and guidance toward the grasp of principles, with the problems of health and disease as a frame of reference, the student will build the necessary foundation for his career in medicine, be it practice (general or limited), teaching, research or administration.

"In working toward this fundamental objective, undergraduate medical schools must strive to help the student to: acquire basic professional knowledge; establish essential habits; attain clinical and social skills necessary to the best utilization of that knowledge; and develop those basic intellectual attitudes, and ethical or moral principles which are essential if he is to gain and maintain the confidence and trust of those whom he treats, the respect of those with whom he works and the support of the community in which he lives.

"These . . . aims are obviously not distinctly separable, but are mutually interdependent. All together they summarize the desirable characteristics of the responsible professional person medical education is attempting to produce."

Organization and Administration

A. *Governing Body.* A medical school should be incorporated as a nonprofit institution, if possible as

a part of a university, since a university can so well provide the milieu and support required by a modern medical school.

If not a component of a university, a medical school should have a board of trustees composed like that of a university of public spirited men or women having no financial interest in the operation of the school or its associated hospitals. The trustees should serve for fairly long and overlapping terms.

Officers and faculty of the school should be appointed by the board of trustees. In keeping with generally accepted principles of administration, it is usually not desirable for a member of the board of trustees to serve simultaneously as an administrator or a member of the faculty of the medical school.

The manner in which the medical school is expected to conduct its affairs, including the responsibilities and privileges of administrative officers, faculty, and students, should be clearly indicated in by-laws approved for the medical school itself or adequately presented in the by-laws of the parent university.

B. *Administrative Officers of the Medical School.* There should be competent supervision of the medical school by the dean or other executive officer who, by training and experience, is qualified to provide leadership in interpreting high standards in medical education, and who has sufficient authority to implement such standards. The dean should have the respect and support of the faculty and ready access to the university president and other officials. The establishment and maintenance of a congenial and productive relationship with the local medical profession is desirable and important to the school and the profession. It can be best assured through discussions of mutual problems by representatives of the school and practicing profession.

Because of the diverse and heavy responsibilities placed upon the dean or executive officer, assistance by suitably qualified persons should be provided. In many medical schools, for example, there is an assistant dean who devotes major attention to student affairs and another assistant for administering the postgraduate program. In the conduct of the fiscal affairs of the school, the dean should have the assistance of a capable business officer.

C. *Faculty Organization.* The faculty should be organized into suitable departments representing the major basic science and clinical fields. It is to be noted that this is primarily an administrative convenience; it should not form the sole basis for structuring the curriculum. Each such department should have a voice, through appropriate committees of the faculty, in the administration of the academic affairs of the school. Foremost among these should be an executive committee of the faculty composed primarily of the responsible administrative officials and the chairmen of those departments which have a major role in the educational program. Usually these are Anatomy, Physiology, Biochemistry, Microbiology, Pharmacology, Pathology, Medicine, Surgery, Pediatrics, Obstetrics-Gynecology, Psychiatry, and Preventive Medicine, and Public Health. This commonly utilized pattern allows for balance between basic science and clinical viewpoints in the committee's major function of determining, with the dean, medical school policies for consideration, where indicated by higher university authority.

There should be such committees of the faculty as admissions, promotions, curriculum, postgraduate medical education, library, and others needed to serve the welfare of the school.

The entire faculty should meet one or more times annually to provide an opportunity for all faculty members to become acquainted with and to discuss medical school policies and practices.

Nominations for faculty appointments should originate in the faculty under the leadership of the dean. Commonly, nominations for appointments at the lower academic ranks are made by the head of the department concerned, after thorough discussion of the nominees by the entire department. At the professorial and the associate professorial levels this procedure may be profitably supplemented or supplanted by the appointment of a nominating committee composed of members of several departments, whose standing and judgment are generally unquestioned. Recommendations are made to the faculty executive committee and dean who, in turn, recommend to the president and board of trustees through established administrative channels.

D. *Finances.* Experience has established that a medical school cannot successfully carry out its many activities solely on the income derived from student fees. Furthermore, certain of these activities are not directed primarily to the education of the medical student and he should not be expected to support them. To adequately fulfill its obligation, a medical school should have other substantial sources of revenue.

Each department within the school should prepare its budget in consultation with the dean, who is ultimately responsible for the total budget and its presentation to the proper authority.

Faculty

The school should have a competent staff with demonstrated interest and ability in teaching and research. Such dual activity by the faculty is most likely to provide the educational milieu appropriate in a modern medical school as well as best carry out its objectives and responsibilities.

Reasonable security of tenure and possibility of ad-

vancement should be assured in order that the personnel of the faculty may have adequate stability. Compensation of full time members of the faculty should be sufficient to enable them to support themselves and their families.

The number of instructors in each basic science and clinical department should be sufficient to meet the requirements of a modern medical educational program as well as allow adequate time for research by each instructor. Full time teacher-student ratios may vary widely depending on the course content, educational methods, research activities, the availability of competent part time or voluntary staff, and other factors. Recognition of the values of intimate teacher-student relationships and widespread use of methods favoring the active role of the student in his own education have decreased dependence on didactic exercises. Increasing use has also been made of interdepartmental teaching. These factors have tended to increase the relative size of the instructional staff.

The faculty personnel in the basic science disciplines should be almost entirely on a full time basis. In the major clinical areas of medicine, surgery, pediatrics, psychiatry, obstetrics and gynecology, there should be a nucleus of full time instructors who have as their major responsibility the planning and supervision of the department's educational program and the conduct of research.

Students

The admission of students to a medical school should be the responsibility of a committee of the faculty. Decisions regarding admission should be based not only on satisfactory prior scholastic accomplishment but also on such factors as personality and emotional characteristics, motivation, industry, resourcefulness, and health. Evaluation of these factors should be developed through personal interviews, college records of academic and nonacademic activities, results of medical college admission tests, and pertinent letters of recommendation. All records dealing with admissions should be carefully filed and procedures periodically reviewed in a search for better methods.

At least three years of college education is required for most students and four years is recommended as a preparation for medical study. Only rarely and under exceptional circumstances will a medical school be justified in admitting a superior student after two years of college study. The National Committee of Regional Accrediting Agencies maintains a listing of institutions of higher education which have been found to offer commendable educational programs. Prospective medical students should acquire their preparatory education at a college of arts and sciences so listed and a medical school admissions committee should scrutinize with particular care the qualifications of applicants whose preparatory study has been done at other institutions.

Because basic knowledge of biology, physics, inorganic and organic chemistry and human behavior are the foundation stones of medicine, adequate college courses in these subjects, as well as demonstrated competence in English, should be required. It is important that a medical college restrict its admission requirements to this minimum so that a college student preparing for the study of medicine will have the opportunity to acquire a broad liberal education or to study a specific field in depth according to individual interest and ability. The complexity of modern medicine can be best served by physicians who in composite represent variety of backgrounds in education and experience.

Advanced standing may be granted to students for work done in other medical schools, but only when a student's previous work is qualitatively and quantitatively equivalent to that required of regularly enrolled students, as officially verified by correspondence with the school previously attended. Because of the diversity and greater integration of the total curriculum, transfers are becoming increasingly difficult but usually are least disruptive of the student's education at the end of the second year.

The number of students who can have an adequate education in a medical school is related to the laboratory and hospital facilities available and to the size and qualifications of the teaching staff (see also: Faculty). A close personal contact between students and members of the teaching staff results in a quality of educational experience that is not possible in an institution where the number of students is excessive in relation to the staff and facilities.

There should be a system of student records showing conveniently and in detail the admissions credentials as well as the grades or other records of performance in the school, by means of which an exact knowledge can be obtained regarding each student's work and qualifications. Qualitative evaluations of each student by instructors should be included in the student records.

An adequate provision for student counseling should be in effect. Many schools have an assistant responsible to the dean for such counseling.

There should be an active student health service providing for periodic medical examination and medical care for the student body. This is important not only in the maintenance of student health but also because of its inherent educational values.

Facilities

A medical school should own or enjoy the assured use of buildings and equipment adequate quantitatively and qualitatively to provide an environment most

conductive to productivity of faculty and students in the fulfillment of the total objectives of the school. If possible, all of the basic medical sciences should be housed in a building which adjoins in some manner the clinical facilities so as to promote cooperative teaching efforts and allow all departments ready access to clinical material.

A well maintained and catalogued medical library that can be used conveniently and effectively by both students and faculty is essential to a modern medical school. A trained librarian with experience in medical library work should be employed to supervise the development and operation of the library with the advice and assistance of an active representative committee of the faculty. The library should receive regularly the leading medical periodicals, the current numbers of which should be readily accessible. Adequate arrangements should be made by the librarian and the faculty to instruct all students in the use of the library at the beginning of their medical studies.

The school should own or have the unquestioned right to appoint the attending staff of a general hospital for clinical teaching. In the event that a medical school depends for clinical teaching on an independent hospital, it is essential that the clinical teachers, either on nomination by the school or by agreement in conference between school and hospital, be appointed by the hospital trustees to appropriate positions on the hospital staff.

The teaching hospitals should be either adjoining or in close proximity to the school and should provide sufficient patients to permit students individually to observe, work up, and study the progress of the common variety of medical and surgical cases as well as a fair number of patients in each of the other major specialties.

There should be a sufficient number of patients so that each student on a hospital clerkship can be assigned that number of new cases of teaching value each week for thorough study that the faculty judges to be of maximum educational value. For example, this may be two new patients a week in one department or five new cases weekly in another, depending upon the orientation objectives and teaching program of the department concerned. Therefore, no fixed number of hospital beds or patients per student can be established because of the variables involved. Medical education should emphasize intensive long term study by each student of relatively fewer patients rather than superficial observation of many patients.

The school should own or have unquestioned use of well ordered facilities for the diagnosis, treatment and follow-up of ambulatory patients. The attending staff should be drawn from the faculty including those of senior rank. The number of new cases per day available to each student serving an outpatient clerkship should be compatible with the educational objectives and teaching program of the department as well as the school.

There should be sufficient offices, laboratories, and conference rooms as a part of or conveniently close to the hospital and outpatient clinical facilities to meet the needs of faculty and students. The hospital floors should provide adequate space and facilities for student clerks to study their patients.

Educational Program

Before the curriculum, methods and details of an educational program can be decided, the objectives of the program should be formulated.

The objectives should clearly indicate that an undergraduate medical education provides merely a sound foundation for further education during the internship and residency periods, as well as throughout professional life. Four years of education in medical school is not by itself sufficient to prepare a physician for practice today. In fact, the yearly advances in medicine demand that each physician continue his education throughout his career. It is also obvious that no physician can master the whole spectrum of medical knowledge.

No rigid curriculum can be prescribed for accomplishing the objectives of medical education. On the contrary, it is the responsibility of the faculty of each school continually to reevaluate its curriculum and to provide in accordance with its own particular setting and in recognition of advances in science a sound and well-integrated educational program. Each school should utilize those methods and approaches that the particular interests and abilities of the faculty indicate would provide the most effective education in the framework of the available facilities. The traditionally separate disciplines are finding rewarding educational and research results in working together cooperatively.

Through the various educational methods and to the extent deemed best by the faculty to accomplish the objectives of medical education, each medical school should offer education in the following subjects during the four year curriculum:

Human Anatomy, Biochemistry, Physiology, Microbiology, Pharmacology, Pathology, Clinical Laboratory Diagnosis, Physical Diagnosis, Internal Medicine, Pediatrics, Obstetrics and Gynecology, Preventive Medicine and Public Health, Psychiatry, Radiology, and Surgery. Specialty areas in medicine and surgery are best integrated in the teaching of the major disciplines. Consideration of social, emotional and environmental factors in health and disease is properly the responsibility of all clinical departments. Medical ethics, legal medicine, biostatistics and medical genetics should be included in the educational program.

The traditional emphasis on lectures, demonstrations and amphitheater clinics in which the role of the student is passive has shifted to greater use of individual student and small group projects, conferences, seminars, and the "case method" of education, in all of which the student actively participates in his own education.

The allotment of some unscheduled student time in the weekly program to allow for reading, research or other independent pursuits is desirable.

In the clinical years particularly, there is no substitute for the "case method" of clinical education, in which individual students work up individual patients under guidance in the hospital wards and in outpatient clinics. Such assignments should occupy most of the time and energy of third and fourth year medical students. The student should be encouraged to feel a genuine responsibility as part of a team of physicians studying the patient, and not as a classroom student with prescribed hours of work. The student's work-up of each case including progress notes should become part of the hospital's permanent record of the case. Such case studies should serve as the point of departure for informal conferences, rounds, and reading. Lectures and other didactic exercises cannot replace though they may supplement bedside learning.

Accreditation of Medical Schools

The American Medical Association through its Council on Medical Education and Hospitals and the Association of American Medical Colleges through its Executive Council serve as the recognized accrediting agencies for medical schools. Through retaining their individual identities, both groups work very closely in this activity through the Liaison Committee on Medical Education. To be accredited, a medical school must be considered approved by the Council on Medical Education and Hospitals and offered membership in the Association of American Medical Colleges. This is granted on the finding of a sound educational program as a result of a survey conducted jointly by both organizations.

It is the intent that newly developing medical schools should be surveyed during each of the first four years of active existence. Provisional accreditation is granted, when the program warrants, for the first two years of the curriculum and definitive action is taken during the implementation of the fourth year of the curriculum.

Existing medical schools are surveyed at regular intervals. Every attempt is made to fulfill requests for interim surveys as a consultant service to the medical schools.

A medical school to be surveyed is requested to provide basic information on forms forwarded in advance. After careful study of this material, the survey team of three or four members visits the medical school for three to five days. On completion of its visit, the survey team confers with the responsible administrative officials of the medical school and its parent university, indicating to them the nature of the major findings and recommendations. A complete, written report is prepared and considered separately by the Council on Medical Education and Hospitals and the Executive Council of the Association of American Medical Colleges and then jointly by the Liaison Committee on Medical Education. The action of each group and the complete report is then transmitted to the medical school dean and university president.

Additional data can be obtained from the Secretary, Council on Medical Education and Hospitals, American Medical Association, 535 North Dearborn St., Chicago 10, or the Secretary, Association of American Medical Colleges, 2530 Ridge Avenue, Evanston, Illinois.

Pediatrics Society Meets

The annual meeting of the Kansas Pediatrics Society was held at the Broadview Hotel, Emporia, on September 7. Dr. Theodore E. Young, Winfield, was elected president for 1958, Dr. Hilbert P. Jubelt, Manhattan, was named vice-president, and Dr. Thomas C. Hurst, Wichita, was chosen secretary-treasurer.

Two speakers, Dr. Charles Upton Lowe, Buffalo, New York, and Dr. Michael Furcolow, Kansas City, presented a program with discussions following the lecture periods.

Surgeons Elect Officers

Dr. Orville R. Clark, Topeka, took office as president of the Kansas Chapter of the American College of Surgeons at a meeting held at Great Bend on September 15. Dr. Marion F. Russell, Great Bend, was elected vice-president and president-elect, and Dr. Robert W. Myers, Newton, was named secretary-treasurer. Plans were made for a 1958 meeting to be held in Wichita.

Pharmaceutical Firms Merge

Stockholders of Schering Corporation and White Laboratories, Inc., voted in separate meetings last month to merge the two firms into a single pharmaceutical company. The merger became effective on September 19 with Schering as the surviving corporation.

THE MONTH IN WASHINGTON

Editor's Note. The following summary of Washington news was prepared by the Washington office of the A.M.A. for distribution to state and regional medical journals.

In the last few years interest has built up in the problems of older people—how they are to get their bills paid, how to spend their time constructively, what chronic medical conditions are causing them the most trouble. Innumerable national and local conferences have searched for ways to make life more satisfying and healthy for people entering old age, and committees are at work on the problem in thousands of communities.

In this favorable climate, when every device that might help the older citizens is being examined, there is being revived a scheme that met with no success at all when first proposed more than six years ago.

It is a plan for government-paid hospitalization under the Old Age and Survivors' Insurance system.

Here is the argument that is made for it:

People in old age generally have less income than when they were younger, but at the same time they require more medical attention and hospital care. Neither voluntary nor commercial health insurance has been able to offer these people the protection they need. The only solution, sponsors of the plan say, is to get the federal government into the picture.

Opponents of the idea agree that older people are sick more often and generally don't have much money, but they disagree violently with the other arguments. They point out that slowly but surely insurance coverage is being extended to older people at a price they can afford to pay. Most important, hospitalization-at-65 critics maintain that a system like this is in effect national compulsory health insurance under Social Security.

Early this year Reps. Emanuel Celler (D., N. Y.) and John Dingell (D., Mich.) introduced bills on this subject. They would allow 60 days a year free hospitalization for OASI-covered men 65 and over and women 62 and over. Rep. Kenneth A. Roberts (D., Ala.) offered a similar bill.

Just before the session ended two developments occurred that are evidence the proponents of this system of hospitalization are getting ready to make a real fight for it next year.

First, Rep. Aime J. Forand (D., R. I.) presented a bill that would make extensive liberalizations in the social security program, including creation of a hospitalization that would give free surgical service to the aged program. Some national labor leaders immediately pledged their support to this bill, a not unexpected move as the AFL-CIO is officially behind the general idea.

Then Senator Richard L. Neuberger (D., Oregon) made it plain he, too, wanted the old people to have free in-hospital medical care. The senator said he hadn't firmed up his thoughts, but that he believed the best approach would be something like the Military Dependent Medical Care program (Medicare), making use of Blue Cross or other nonprofit groups. He estimates that a 1 per cent increase in payroll taxes for both employer and employee would meet the extra costs.

Mr. Forand, on the other hand, is specific. He would make all persons receiving OASI retirement benefits eligible and also surviving widows and children, but would not include persons receiving OASI disability payments. He would broaden the time period by allowing 120 days of hospital or nursing home care each year, with hospital stays limited to 60 days.

The Forand measure also has a provision, not contained in most earlier bills, for OASI also to pay for in-hospital surgical services certified as necessary by the physician.

Mr. Forand would take no chance of running out of money. He would levy social security payroll taxes on all income up to $6,000 (present limit $4,200), and also increase the tax rate a half per cent for employer and employee alike, and three-quarters of one per cent for the self-employed.

It is almost certain that these and other similar suggestions will receive serious consideration by Congress next year, with passage of a bill much more likely than in 1951 when President Truman and Oscar Ewing first proposed the idea.

Notes

When Congress returns January 7, one of the measures waiting its attention will be a bill to control union welfare funds through registration and publicity. (Most funds involve medical-hospital benefits.)

Jenkins-Keogh legislation, for deferment of income taxes on money put into retirement plans by the self-employed, now is assured of a hearing next year when the House Ways and Means Committee goes into all phases of taxation.

American Medical Association is cooperating with American Hospital Association in an effort to persuade the Federal Communications Commission to set aside radio channels for exclusive use of doctors and hospitals.

Tumor Conference

Multiple Eosinophilic Granulomas of Bone

Edited by Howard P. Fink, M.D.

Dr. Stowell (Moderator): This case illustrates an uncommon type of bone lesion which is not generally regarded as neoplastic but which is confusable, clinically and radiographically, with a number of neoplastic diseases.

L. W. Akers (Junior Medical Student): The patient is a 22-month-old white boy who was first admitted to this hospital three weeks ago because of irritability and lumps on the head. He had been in good health until about 11 months prior to admission when he had a severe crusting dermatitis of the scalp. This was diagnosed as cradle cap and treated with various medications without much relief. The dermatitis was considerably improved when, about five months prior to admission, he had some sort of trauma to his forehead, followed by the appearance of a persistent lump at the site of injury. This lump did not progress in size. An x-ray was taken of the skull about a month later, and two radiolucent spots were noted in the skull beneath the lump. It was believed then that the patient had an abscess of the skull. He was treated with antibiotics, but no regression of the swelling resulted. During the following four months, the patient sustained several other minor episodes of head trauma, followed by indolent swellings. Blood counts done during this time at another hospital revealed iron-deficiency anemia. The boy had an intermittent low-grade fever for a week or two prior to his admission here.

The past history and family history are not remarkable. System review is essentially negative, except for the fact the child has become increasingly irritable during the past year.

On admission the boy appeared well-developed, well-nourished, and somewhat irritable. There were four or five soft, non-fluctuant, tender subcutaneous swellings on the head, ranging in size from 2 to 6 cm. in diameter, which showed no evidence of acute inflammation. A few of these lesions were somewhat depressed in the center. Venous dilatation was present in the skin overlying the swellings. A few small cervical nodes were palpable. The liver edge was felt about one finger below the costal margin. The spleen was perhaps slightly enlarged. The rest of the physical examination was negative.

The urine was normal. The hemoglobin was 10.6 grams; the white blood count was 8100, with 42 filamented and 13 non-filamented neutrophils, 1 eosinophil, 40 lymphocytes, 3 monocytes, and 1 metamyelocyte. The platelet count was 92,000. Bleeding time was one minute and clotting time 4 minutes. Blood glucose was 79 mgm. per cent, serum albumin 3.82 gm. per cent, serum globulin 1.68 gm. per cent, cholesterol 129 mgm. per cent with 69 per cent esters. Sternal marrow biopsy showed hyperplasia of the marrow, particularly erythroid hyperplasia and eosinophilia. The marrow contained scattered macrophages, some of which had foamy cytoplasm. Two biopsies of the head lesions were also done, and extensive x-ray studies were made.

Dr. Boley: Did each swelling appear after a specific trauma?

Mr. Akers: The history is vague on that point; but the boy's mother enumerated several episodes of mild injury, each followed by a lump.

Dr. Tice: Does the patient have any exophthalmos?

Mr. Akers: No.

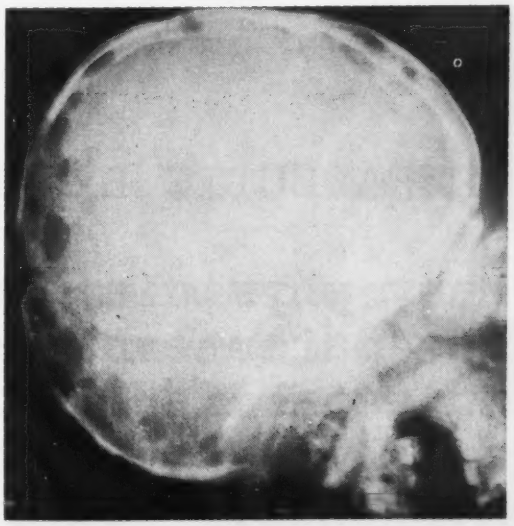


Figure 1. Roentgenogram showing multiple rounded radiolucent areas in cranial vault.

Cancer teaching activities at the University of Kansas Medical Center are aided by grants from the National Cancer Institute, U. S. Public Health Service, and the Kansas Division of the American Cancer Society. Dr. Fink is a Trainee of the National Cancer Institute.

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Dr. Stowell: Would you discuss the x-rays, Dr. Goertz?

Dr. Goertz: In the skull plates many irregular radiolucent foci are easily seen (Figure 1). Most of these are in the frontal and the anterior parietal areas, but a few are present in the occipital region as well. In the antero-posterior view, rarefaction is also seen in the floor of the right orbit and in the right petrous pyramid.

In the chest films, the heart and lungs appear normal, but numerous areas of radiolucency are present in the ribs. Similar areas can be seen in the pelvis and in both femurs. There is slight enlargement of the liver and spleen. No lesions of the upper extremities are discernible.

The radiographic diagnosis was reticuloendotheliosis. Metastatic neuroblastoma was considered as a secondary possibility.

Dr. Tice: I think many disease processes which can give rise to multiple osteolytic lesions of bone must be thought of in the differential diagnosis in this case. In view of the patient's age, certainly the two most likely possibilities are reticuloendotheliosis of the Letterer-Siwe or eosinophilic granuloma type, and the Hutchinson pattern of metastases from a neuroblastoma of the adrenal. The latter lesion is not ruled out by the absence of proptosis and lymphadenopathy. Polyostotic fibrous dysplasia of bone is rare in this age group, and the patient does not have the endocrine disturbances and cafe-au-lait skin spots characteristic of this disease. If the patient were an adult, multiple myeloma, osteitis fibrosa cystica, and metastatic carcinoma, especially from a carcinoma of the lung, kidney, thyroid, or breast, should be given prime consideration.

Dr. Stowell: Dr. Helwig, what does the biopsy of the skull lesion show?

Dr. Helwig: The tissue contains no bone; it consists of a helter-skelter mixture of histiocytes, eosinophils and lymphocytes, constituting the classical picture of eosinophilic granuloma of bone. Immense numbers of massed eosinophils can be seen in some areas.

A feature of special interest in this case is the multiplicity of the lesions. Eosinophilic granulomas of bone are multiple in 20 to 60 per cent of cases; the figure varies with the investigator. Probably a good many multiple lesions are overlooked because of lack of complete skeletal surveys on patients with supposedly single eosinophilic granulomas. In order of frequency, the ribs are involved most often, the scapulae second, the ilia third, the femurs fourth, and the skull fifth. The disease is most frequently seen in infants and children, but it occasionally occurs in adults, even those of middle age and older. Both single and multiple lesions may be accompanied by mild fever and slight leukocytosis, sometimes with an excess of circulating eosinophils. I believe the present case showed eosinophilia in the sternal puncture specimen, though not in the peripheral blood.

Dr. Diehl: I might add that the lesions tend to be multiple in infants and single in older children and adults, though this is not an absolute rule.

Certainly the histologic picture that Dr. Helwig has outlined for us in this case is typical of eosinophilic granuloma. However, I wish to ask the pathologists what the possibility is that this disease process may later develop into Hand-Schüller-Christian's or Letterer-Siwe's disease, what the relations are among these three entities, and whether other organ systems besides the bones can be involved by eosinophilic granuloma. These questions are of great importance in determining this child's prognosis.

Dr. Mantz: They are also exceedingly difficult ones, and I am sure it would be hard to find two pathologists who agree absolutely on the answers. I believe that most investigators now accept these three diseases as different manifestations of one essential process, that of excessive proliferation of reticuloendothelial cells, or reticuloendotheliosis. Although the hyperplasia sometimes seems to have no natural limit, most pathologists are unwilling to consider the process a neoplastic one. Letterer-Siwe's disease, however, does have some features in common with the lymphomas. The proliferated cells in the Hand-Schüller-Christian syndrome for the most part retain their normal function, that of phagocytosis; while in the Letterer-Siwe syndrome they do not. Phagocytosed material, if present, consists of lipid; but the proliferation, not the phagocytosis, appears to be the essential feature, so that none of these conditions can properly be considered a lipid storage disease. Lichtenstein[1] has recently clarified and restated this concept; he refers to this group of syndromes as "histiocytosis X," and suggests that a given case may be diagnosed more specifically as "histiocytosis X with manifestations of" Letterer-Siwe's disease, Hand-Schüller-Christian's disease, or eosinophilic granuloma.

The present case illustrates well the close interrelationship of these three syndromes. As Dr. Helwig has said, the biopsy specimen is a classic example of eosinophilic granuloma; but the history of anemia, fever, a cutaneous eruption, and slight hepatosplenomegaly suggests systemic involvement, which in turn inclines one to the diagnosis of subacute Letterer-Siwe's disease. According to prevailing opinion, the latter disease carries a fatal or at least a grave prognosis. However, this gloomy outlook may well

be altered in the near future. I recall a child who had the classical signs, symptoms, and pathological changes of Letterer-Siwe's disease. His parents were frankly told to expect him to become debilitated and die in a short period of time. Several years later, when an attempt at follow-up was made, the child was found to be in excellent health. Such a case as this indicates that we should either revise our diagnostic criteria for Letterer-Siwe's disease, or else give up the belief that it is a universally fatal condition.

Most monostotic, and even many polyostotic, eosinophilic granulomas will regress and eventually heal completely if treated with x-ray. Some progress, with or without remissions, to the multiple xanthomatous lesions of Hand-Schüller-Christian's disease. In still other cases, resembling the one under discussion today, the Letterer-Siwe syndrome eventually develops; the reticuloendothelial proliferation becomes widespread, with little or no lipid storage, and ultimately death results. Present understanding of these diseases is so incomplete that in a given case I think only the patient's subsequent course reveals the final answer.

In reply to Dr. Diehl's last question, I can say that many cases of eosinophilic granulomas in organs not usually considered part of the reticuloendothelial system have been reported, most of them in the lung, and most of them associated with widespread involvement of bones.

Dr. Tice: Dr. Mantz, what is the present concept of the relation between histiocytosis X and such conditions as Niemann-Pick's and Gaucher's diseases?

Dr. Mantz: These are still generally regarded as true lipid storage diseases which are due to an inborn error of lipid metabolism, resulting in the piling-up of large quantities of lipid in reticuloendothelial cells. In Niemann-Pick disease the stored lipid is largely sphingomyelin, while in Gaucher's disease it is a cerebroside. In the Hand-Schüller-Christian syndrome, cholesterol deposition in the proliferated reticuloendothelial cells is prominent; but according to Lichtenstein the cholesterol analogue of Niemann-Pick's and Gaucher's diseases is not the Hand-Schüller-Christian syndrome, but xanthoma tuberosum multiplex. In other words, histiocytosis X differs fundamentally from these storage diseases.

Dr. Diehl: The sternal puncture specimen, as I recall, contained a few foamy macrophages and more than the expected number of eosinophils. Do you suppose this represents diffuse involvement of the marrow, or did the needle enter a localized lesion by chance?

Dr. Mantz: The x-rays show no rarefaction of bone at the site of the sternal biopsy, but still an early eosinophilic granuloma may be present in this region. I don't think your question can be answered on the basis of a single puncture.

Dr. Stowell: Dr. Olson, what treatment is this child receiving?

Dr. Olson: We considered that the multiplicity of the lesions contraindicated enucleation or any other surgical procedure. At present, x-ray is the only therapy we plan to use.

Dr. Tice: We contemplate giving the child approximately 1,000 roentgens over each area involved: skull, ribs, pelvis, and femurs. The dosage to each region must be delicately adjusted, and we have been careful to warn the parents that the boy will lose his hair temporarily. I cannot recall having seen an eosinophilic granuloma fail to respond to x-radiation, and I think we can confidently expect considerable regression, although I must admit I am extremely doubtful of permanent cure in this case.

Dr. Helwig: Dr. Tice, isn't there a chance that 1,000 roentgens, given through each of several ports, will damage bony epiphyses and lead to arrest of bone growth?

Dr. Tice: Yes, unless adequate care is used to shield the epiphyses from the radiation. Also, great pains must be taken to prevent injury to the gonads when the pelvis is irradiated.

Dr. Boley: The biopsy which Dr. Helwig has discussed was the second taken from this patient. The first, also of a skull lesion, showed nothing suggestive of an eosinophilic granuloma; it consisted solely of fibrous tissue which was somewhat more vascular than one expects in scar tissue. At the time this first specimen was taken, the child had received no x-ray or other definitive therapy. Hence, these lesions can undergo spontaneous involution; and if this is so, it improves this patient's prognosis considerably. Some such process must have been responsible for the spontaneous cure in the case that Dr. Mantz mentioned.

Dr. Stowell: This is an encouraging observation, at least so far as this particular patient is concerned.

This case has been presented as an example of a condition which must be considered in the differential diagnosis of multiple radiographic defects of bone.

Reference

1. Lichtenstein, L.: Histiocytosis X, A.M.A. Arch. Path. 56:84 (July) 1953.

One good sneeze can send 20,000 infection-laden droplets shooting as far as 12 feet, at a speed of 150 feet per second. Even after half an hour, cautions the Kansas State Board of Health, 4,000 of them will still be in the air.

PHYSICIANS' ACTIVITIES

Dr. James T. Moy has returned to practice in Wichita after completing a course in cardiovascular disease at Harvard Medical School.

Dr. and Mrs. C. Omer West, Kansas City, are enjoying a trip abroad with a stop in Istanbul, Turkey, to attend the 11th General Assembly and the 30th Council Session of the World Medical Association.

A talk on "Surgery for Peptic Ulcer" was given by **Dr. Lloyd W. Reynolds,** Hays, at a recent meeting of District 9 of the Kansas State Nurses' Association.

Dr. James J. Basham, Fort Scott, has been named health officer of Bourbon County, succeeding **Dr. J. R. Pritchard,** Fort Scott, who had previously accepted a temporary appointment.

Plans to move to Detroit, Michigan, were announced recently by **Dr. Lawrence E. Filkin,** who has practiced in Concordia since 1946. He will be practicing in the medical division of the Ford Motor Company in Detroit.

Dr. Rodger A. Moon, Kansas City, served as moderator of a discussion on mental health at a Camp Fire Girls conference at Lake Quivira last month.

An announcement was made recently by **Dr. William V. Hartman,** Pittsburg, that he will move to St. Louis. He had practiced in Pittsburg for 45 years.

Dr. William R. Jones, Canton, went to Detroit, Michigan, recently to take part in a postgraduate program offered by Parke-Davis and Company.

Dr. Harry Lutz, Augusta, discussed the Butler County health program at the annual Butler County Teachers' Institute in El Dorado at the opening of school.

"The Present Status of Our Knowledge About the Group of Schizophrenias" was the subject studied at the Second International Congress for Psychiatry at Zurich, Switzerland, last month. One of the participants was **Dr. Karl Menninger,** Topeka.

Dr. James B. Pretz, Kansas City, spoke on "Rest and Fatigue" at a public meeting at Donnelly College, Kansas City, recently. His discussion was one of a series on the subject of "Improving the Health of the Community."

A ten-week trip to Europe was concluded recently by **Dr. Edward J. Grosdidier,** Kansas City. He was accompanied by Mrs. Grosdidier and their three daughters.

Dr. DeMerle E. Eckart, Hutchinson, has received word from the National Institute of Health that a progress report of his theory entitled "A Wave Theory of Nervous System Function" will be included in its collection of developments in the field of psychopharmacology.

A talk, "Education for Childbirth" was given by **Dr. Gerhart R. Tonn,** Wichita, before the Sedgwick County Medical Assistants' Society at its September meeting.

Dr. Clarence H. Benage, Pittsburg, was made a fellow of the International College of Surgeons at a convocation held in Chicago in September.

Dr. Robert W. Hughes and **Dr. Wendale E. McAllaster,** Russell, who have been spending three afternoons a week practicing in Natoma, have announced plans to discontinue the Natoma practice, effective October 1.

"Fractures and Dislocations of the Cervical Spine" was the subject of a paper presented by **Dr. John F. Thurlow,** Hays, at a meeting of the Kansas Chapter, American College of Surgeons, on September 15. **Dr. Charles Isaac,** Newton, spoke on "Urological Anomalies Coming to Surgery."

Dr. Victor G. Henry, Jr., Newton, discussed hypnosis before a recent meeting of the Harvey County Medical Assistants' Society.

Plans to close his office in Douglass have been announced by **Dr. Frederick F. Lemon,** who will spend the winter in Salina with a daughter.

Dr. Maurice A. Walker, Kansas City, was the subject of a feature story published in the *Kansas City Kansan* on September 15.

Declining mortality from tuberculosis since 1900 has had its greatest impact among young adults (ages 15-44) in the peak income and childbearing years, according to Health Information Foundation. The highest mortality from this disease now occurs in the upper age grades among those over 65.

COUNTY SOCIETIES

The Sedgwick County Medical Society began its 1957-1958 year with a golf and skeet tournament, followed by a banquet, at the Rolling Hills Country Club, Wichita, on September 20. The first scientific program of the season was presented on October 8.

Dr. William V. Hartman, who had practiced in Pittsburg for 45 years before moving to St. Louis, was guest of honor at a dinner meeting of the Crawford County Medical Society last month. Wives of members were also guests, making an attendance of 60. Dr. Clarence H. Benage served as toastmaster and presented a gift from the group.

A special meeting of the Leavenworth County Society was held in Leavenworth recently to discuss plans for administering vaccine for Asian influenza. The group voted to follow the priority system outlined by the United States Public Health Service, allocating the first supply of vaccine for hospital workers, then police, fire and transportation workers, and, third, essential industrial workers.

Residents of Washington County were guests of the medical society there on September 17 for a special showing of the Smith, Kline and French Laboratory film, "Mongana," a record of the daily experiences of a medical missionary and his family in the heart of Africa.

A joint meeting of the Wyandotte County Medical Society and the Wyandotte County Bar Association was held at the Town House, Kansas City, on September 17. The program was devoted to medical, engineering, and legislative aspects of the traffic accident problem.

Physical examinations for members of the Leavenworth High School R.O.T.C. unit and football squad were given last month by 20 members of the Leavenworth County Medical Society. Approximately 200 youths were examined.

The first fall meeting of the Shawnee County Society was held in Topeka on September 3. Dr. Otto Hanson spoke on "Clinical Uses of Radioisotopes." At the business session the group approved single memberships in Blue Cross-Blue Shield for students at Washburn University, approved a reduction in membership fee for physicians in residency training, and elected one physician to membership, Dr. Lewis Wesselius of the Menninger Foundation.

Three Neodesha physicians were elected as officers of the Southeast Kansas Medical Society at a meeting held in Chanute last month. Dr. Charles E. Stevenson was named president, Dr. Frank A. Moorhead, vice-president, and Dr. Glen M. McCray, secretary-treasurer. Dr. Michael Bernreiter, Kansas City, Missouri, was guest speaker.

Dr. Barrett A. Nelson, Manhattan, president of the Kansas Medical Society, addressed the Iroquois Medical Society at a meeting held in Meade on September 9. Members of the Auxiliary were also guests of the medical society.

Members of the Cherokee County Medical Society were guests of the Cherokee County Bar Association at a dinner meeting held in Baxter Springs last month. A film, "The Medical Witness," was shown.

Dr. Vernon M. Lockard, radiologist at Mercy Hospital, Independence, was speaker at a meeting of the Montgomery County Medical Society in Coffeyville last month. His subject was "Cancer of the Cervix."

To Hold Hertzler Memorial Symposium

The first annual Hertzler Memorial Symposium will be held at the Hertzler Clinic, Halstead, on Saturday, November 2. The program will be devoted to a study of thyroid disease. A social hour at 5:00 o'clock will be followed by a buffet supper at 6:00 and a panel discussion at 7:00. All members of the Kansas Medical Society are invited to attend, and advance reservations are requested.

Participants in the discussion will be: Dr. Christian A. Hellwig, Dr. Victor E. Chesky, and Dr. Emmett N. McCusker, all of the Hertzler Clinic; Dr. Arthur Grollman of Southwestern Medical School, Dallas; Dr. Edward Hashinger of the University of Kansas School of Medicine, Kansas City; Dr. George Clayton of Baylor University, Houston; Dr. D. L. Tabern, head of Division of Radioisotopes, of Abbott Laboratories; Dr. Homer L. Hiebert, Topeka, and Dr. Frank E. Hoecker of the University of Kansas, Lawrence.

In 1900 influenza and pneumonia took a toll of 80 persons per 100,000 population in the young adult ages (15 to 44), according to Health Information Foundation. By 1955 mortality from these causes had dropped to around 4 per 100,000 persons in the same age group.

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ANNOUNCEMENTS

Second Cruise Congress, Pan American Association of Ophthalmology, on board *S. S. Queen of Bermuda* with one day each in Puerto Rico, the Dominican Republic, Jamaica, Haiti and Nassau, February 1-14, 1958. Reservations may be made through Mr. Leon V. Arnold, 33 Washington Square West, New York 11, New York.

Part I examinations for candidates for certification by American Board of Obstetrics and Gynecology, various parts of U. S. and Canada, January 2, 1958. For information write the secretary, Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6, Ohio.

The Sister Elizabeth Kenny Foundation announces a continuance of its postdoctoral scholarships to promote work in the field of neuromuscular diseases. Each grant provides a stipend of from $5,000 to $7,000 a year for a five-year period. Write Dr. E. J. Huenekens, 2400 Foshay Tower, Minneapolis 2, Minnesota.

Intensive course in radioactive isotopes offered by Department of Radiology, New York University Post-Graduate Medical School. May be entered the first of any month during academic year. For internists, radiologists, and hematologists. Tuition is $150. Write Associate Dean, 550 First Avenue, New York 16, New York.

American Goiter Association offers Van Meter Prize Award of $300 and two honorable mentions for best essays on problems relating to thyroid gland. Deadline February 1, 1958. Write the secretary, 149½ Washington Avenue, Albany 10, New York.

Courses offered in December by New York University-Bellevue Medical Center: December 2-4, Recent Advances in Diagnosis and Treatment of Poisonings; December 2-4, Infertility; December 2-6, Surgery of the Cornea; December 2-14, Bronchoesophagology and Laryngology; December 2-6, Pediatric Cardiology.

American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois, offers three prizes, $500, $300, and $200, for best essays on any phase of the diagnosis and treatment of chest disease (heart or lungs). Closing date April 15, 1958.

Fourth International Conference on Goiter, sponsored by London Thyroid Club and American Goiter Association, London, England, July 6-8, 1960. A few honoraria available for travel assistance. Write Dr. John C. McClintock, 149½ Washington Avenue, Albany 10, New York.

BLUE SHIELD

Ever since the birth of the "Blues," the big news has been their astounding rate of growth. Blue Cross and Blue Shield have "hit the jackpot" in public acceptance. Blue Cross is now well past the 50 million mark, and Blue Shield expects to pass 40 million by the end of 1957.

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Fourth, the greater the number of his patients covered by prepayment, the fewer for whom the doctor has a collection problem, and the lighter his load of free or part-pay work.

Medicine's most significant benefit from the growth of Blue Shield is the dominant influence of the medically guided Blue Shield Plans on the shape and destiny of the voluntary health insurance movement as a whole. Were it not for Blue Shield, the medical profession would have no effective control over the basic economy of private practice.

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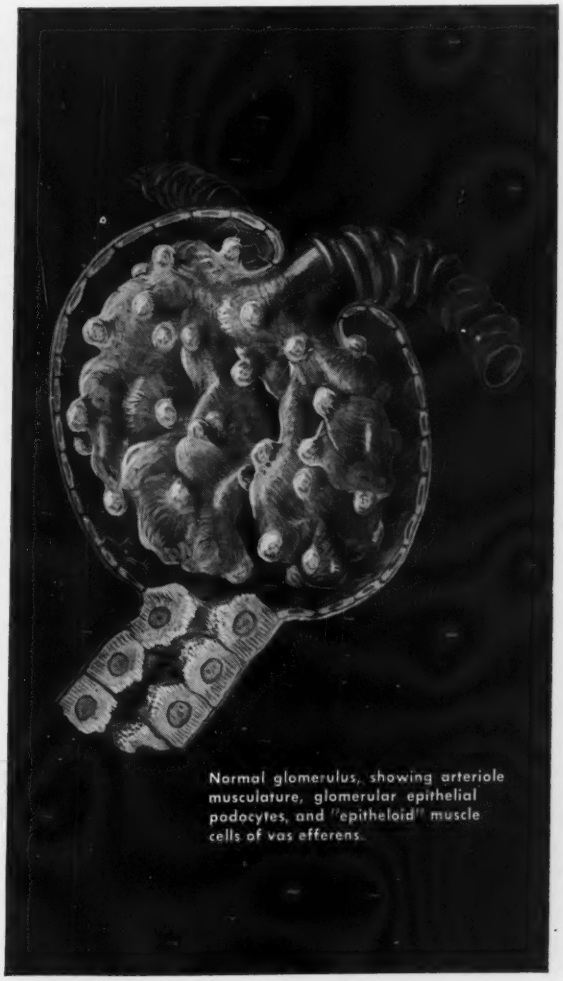
1. Settel, E.: Rolicton® (Aminoisometradine), a New, Nonmercurial Diuretic, Postgrad. Med. *21*:186 (Feb.) 1957.
2. Assali, N. S.: Personal communication, May 28, 1956.



Normal glomerulus, showing arteriole musculature, glomerular epithelial podocytes, and "epitheloid" muscle cells of vas efferens.

SEARLE

The Adenoviruses

Their Relationship to Acute Respiratory Infections

WAYNE E. FRAZIER, M.D., ***St. Petersburg, Florida***

Respiratory diseases, according to several surveys, constitute the most common cause of illness in various population groups in this country. In the great proportion of cases, this large group of respiratory infections is of undetermined etiology, with known bacterial, fungal, and viral agents causing only a relatively small number of the total illnesses.[11]

The problem of classification of various infections of the respiratory tract is indicated by the large variety of names given to illnesses included within this group. Among these respiratory diseases of unknown etiology are the common cold, nasopharyngitis, laryngitis, common respiratory disease, grippe, catarrhal fever, febrile catarrh, acute respiratory disease, tracheitis, bronchitis, and primary atypical pneumonia. Many of these terms have arisen from the prominence of certain symptoms or signs at specific sites of the respiratory tract, and they are of only limited value in defining separate entities. The picture is confused by the fact that different agents may produce the same clinical type of illness, while a single agent may induce variable clinical manifestations resembling almost any of the common respiratory tract diseases.[11, 42]

Recently, through the work of several groups of investigators studying this important problem, a new group of viruses has been discovered inhabiting the respiratory tract. These viruses have been proved to be etiologically related to certain of the clinical syndromes of respiratory tract disease which fall in the large class of those of undetermined cause. The newly-isolated viral agents, however, do not have any apparent causal relationship with the common cold by clinical, serological, and epidemiological studies.

Terminology has been an obstructive problem with this new group of viruses, with clarification arriving only recently, in May of 1956. At that time, the early investigators and others interested in this field met to discuss a solution to the difficulty of nomenclature.[14] Prior to this date, each separate group of investigators who had isolated and studied members of the group of viruses named them independently. To add further to the confusion, the workers ordinarily used abbreviations of the names when discussing their own specific viral agent. Thus, terms such as "adenoidal degenerating" (AD) agents, "acute respiratory disease" (ARD) viruses, "respiratory infection" (RI) viruses, and "adenoidal-pharyngeal-conjunctival" (APC) viruses appeared in research reports. One virologist even suggested that the group should be called the "Hudihi or Hidihu" viruses, to recognize the work of Huebner, Dingle, and Hilleman in this field.[42]

To standardize the nomenclature, various interested men studying these agents agreed on the new term of "adenovirus group" for a collective name. This designation indicated both the characteristic involvement of lymphadenoid tissue and the tissue of first reported isolation.[14, 42] Although the committee which agreed on the name had no official status in matters of nomenclature, the term was accepted among investigators most concerned with the work.

Discovery of the Adenoviruses

During World War II, the Commission on Acute Respiratory Diseases of the Army Epidemiological Board described an acute febrile respiratory infection in recruits. This illness was differentiated from other common respiratory diseases, such as the common cold, streptococcal pharyngitis and tonsillitis, and primary atypical pneumonia, by clinical symptomatology and immunological studies. The disease entity, termed "acute respiratory disease" (ARD) was considered to be caused by a viral agent, but isolation of a virus in experimental animals and chick embryos was unsuccessful.

In 1945, transmission studies in human volunteers were performed, using as inocula the filtered secretions of the respiratory tract from donors with symptoms of common respiratory diseases. It was found that ARD was transmissible, having an average incubation time of five to six days. The importance of this influenza-like syndrome, which occurred in epidemic fashion in the military population, stimulated further investigation of the disease.

An epidemic of ARD occurred at Fort Leonard Wood, Missouri, during the winter of 1952-1953. There were many patients with influenza "A" and also a number of patients with clinical and x-ray

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This is one of a group of theses written by fourth year students at the University of Kansas School of Medicine, selected for publication by the Editorial Board from a group judged to be the best by the faculty at the school. Dr. Frazier is now serving his internship at Mound Park Hospital, St. Petersburg, Florida.

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findings of primary atypical pneumonia during the period of the ARD epidemic. Hilleman and co-workers[20, 22] isolated five cytopathogenic agents from certain non-influenzal cases at the Army post. One of these agents, isolated in HeLa cell culture from a patient with primary atypical pneumonia (Case 67), was designated as the respiratory infection agent No. 67 (RI-67). This new agent was studied in tissue culture, tested serologically, and inoculated into laboratory animals. The workers demonstrated immunologically that the RI-67 agent differed from other virus groups which cause respiratory infections. They also showed that during the epidemic patients with respiratory symptoms not caused by influenza virus developed an increase in titer to the RI-67 virus.

Further studies with the RI-67 agent were reported by Dingle and others[10] in 1954. They demonstrated that the agent was related to cases of ARD that had occurred in recruits at various Army posts during World War II. These workers performed serological studies with sera from these recruits, which had been stored since the time of their illness in 1942-1945. They concluded that ARD was apparently a distinct clinical entity, with a viral agent as the presumed cause, and that RI-67 might be the principal etiologic agent for ARD.

Meanwhile, in 1953, another group of investigators (Rowe and others)[36] reported the isolation of a new cytopathogenic agent from human adenoid tissue. The workers had obtained the tissue from hospital operating rooms following adenoidectomies. They had planned to use the tissue for culture purposes. To their surprise, however, the adenoid tissue underwent spontaneous degeneration in a period of days without ever being inoculated with viral agents. In addition, transfer of culture fluids from the adenoids showing degeneration to fresh tissue cultures would result in characteristic cytopathogenic changes. These changes differed from those produced by other human viruses when inoculated into tissue cultures.

Further studies indicated that the agent was probably a virus, and the investigators proposed the name "adenoidal degeneration" (AD) agent. At this time, the relationship of the newly discovered virus to clinical disease was unknown. Further research was undertaken, therefore, to determine the possible role of the AD virus in human disease, particularly in upper respiratory tract infections.

The group of investigators at the National Microbiological Institute[24] found that many strains of respiratory-system viruses, isolated from nasopharyngeal and conjunctival secretions and feces of persons with respiratory illnesses, were biologically and serologically related to their previously-discovered AD agent. They were able to segregate the 143 strains of the virus into six types, immunologically, and demonstrate human antibody responses to all six types.[35] These workers felt that the term "adenoid-degenerating" agent, which they had proposed originally, was now inadequate. Therefore, they designated these new viruses as "adenoidal-pharyngeal-conjunctival" agents, to indicate the important anatomic sites in which they had been found.

Continuing their investigation of these viruses, they were able to demonstrate by epidemiologic studies that viruses of all six types produced frequent infections in man. In particular, the Types 3 and 4 viruses were incriminated as causing specific respiratory illness. They found that the RI-67 agent isolated by the Hilleman group[20] was a Type 4 virus, apparently responsible for cases of acute respiratory disease and primary atypical pneumonia in military personnel.

Thus, intensive activity in this field by workers at National Institutes of Health resulted in an interesting finding. A group of viruses, discovered and propagated without any definitely known relationship to disease, was later demonstrated to be related to a previously described clinical syndrome, by epidemiologic studies.[40]

Clinical Manifestations

The clinical features of illness produced by infection with an agent of the Adenovirus group are multiple and variable. Signs and symptoms differ somewhat, depending upon the specific Adenovirus type etiologically involved. Also, as in any illness, only certain features will be present in any one case. Therefore, a composite clinical picture, as compiled by Dascomb and Hilleman from 45 cases hospitalized at Fort Dix, New Jersey,[8] will be presented.

1. Constitutional features: fever, malaise, myalgia, chills, erythema, headache, anorexia, dizziness.

2. Eye, ear, nose, throat: pharyngitis with sore throat, pharyngeal exudate, rhinitis, conjunctivitis, otitis, lymphadenopathy.

3. Respiratory: cough, tracheobronchitis, chest pain, laryngitis, dyspnea, pneumonitis.

4. Gastrointestinal: abdominal pain, nausea, vomiting.

The clinical picture resulting from infection by the Type 3 Adenovirus was sufficiently striking as to be designated by a specific name. Bell and associates[4] termed a communicable disease entity, which they described and studied in 1954, "pharyngoconjunctival fever." Common findings in the disease are fever, pharyngitis, conjunctivitis, and cervical lymph-

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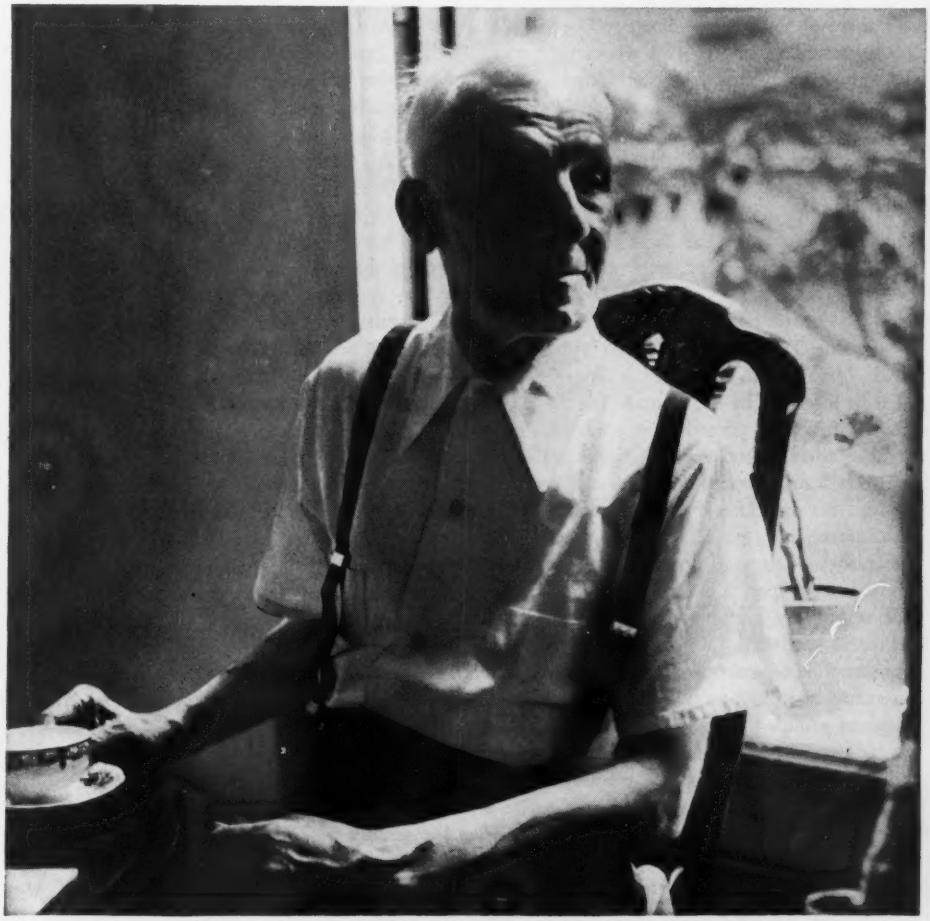

adenopathy. The febrile course usually lasted from five to seven days, with the temperature often spiking to 104 degrees Fahrenheit. Conjunctivitis was frequently monocular, with congestion of the palpebral and bulbar conjunctivae, itching and burning sensations, and conjunctival lymph follicle hyperplasia. The disease occurs most commonly in children. It is apparently highly communicable, with cases occurring in epidemic form from contact in swimming pools.[6, 7, 30, 31, 37]

The Type 4 Adenovirus has been shown to be causally related to the entity termed "acute respiratory disease"[24] in the large proportion of such cases. This infection is an acute, febrile illness characterized by constitutional symptoms of feverishness, chilliness, malaise, headache, and anorexia. In addition, respiratory symptoms of irritated throat, hoarseness, cough, and nasal obstruction are frequently present. Physical findings that are demonstrable include pharyngeal injection, pharyngeal lymphoid hyperplasia, and cervical lymphadenopathy.[11, 16, 17] Patients who are ill with the ARD syndrome usually have the acute episode for three to seven days, often followed by a convalescence period of one to two weeks.

Acute respiratory disease has been found, also, to be associated with Type 7 of the Adenovirus group.[15] The most common presenting features in the epidemic reported by Dascomb and Hilleman[8] were fever, pharyngitis, and non-productive cough. However, the signs and symptoms of ARD, as described in cases caused by the Type 4 Adenovirus, also have been observed in patients suffering with the Type 7 virus infection.

Although conjunctivitis is a common feature of infection with the Type 3 Adenovirus[15] (pharyngoconjunctival fever), this clinical finding is also associated with infection by the Type 6 Adenovirus.[26] A specific eye infection, occurring in epidemic form and termed epidemic keratoconjunctivitis (EKC), was found to be caused by an Adenovirus (Type 8) by Jawetz and his associates.[28] This distinct clinical entity is characterized by a severe keratitis with round subepithelial corneal opacities. In addition, EKC differs from Types 3 and 6 infections by the absence of respiratory symptoms.

The clinical syndrome designated as "primary atypical pneumonia of unknown etiology" has been proved in many cases to be caused by a member of the Adenovirus group. For example, the RI-67 viral agent was originally isolated from a patient exhibiting the clinical and x-ray findings of primary atypical pneumonia. This virus later was discovered to be a member of the Type 4 Adenovirus group. Thus, the clinical picture of primary atypical pneumonia probably can be produced by infection with several different viral agents, including the Adenoviruses. One such agent has been designated as the PAP virus, first isolated in 1944. There is no serological cross-reaction between the PAP virus and the Adenoviruses. Also, the PAP virus induces cold agglutination and Streptococcus MG agglutination, tests which are negative for the Adenoviruses.

Reimann[32] proposes that the term "viral pneumonia" be used for pulmonary lesions caused by such agents as the Adenoviruses rather than the ambiguous and negative term of "primary atypical pneumonia of unknown etiology." He feels that the various infections of the respiratory tract by viruses (PAP, Adenoviruses, etc.) have their own spectrum of severity, ranging from the inapparent or mild attacks, which are most common, to the occasional viral pneumonia.

Laboratory Studies

Since clinical features of illness produced by the Adenoviruses resemble findings that are caused by other agents, the ultimate word for the diagnosis of infection by one of the Adenovirus group is determined by the laboratory.

The cardinal attribute of the Adenovirus group is a common antigen that is demonstrable by complement fixation test.[34] This antigen is not shared with other known viruses, nor do other known infections produce complement fixing antibody against the antigen. The titer of this antigen is determined by testing with a pool of human convalescent serums which have a high titer of complement-fixing antibody to the group antigen.

The specific virus type of the Adenovirus group is identified by the neutralization test. The new serotypes are established by using hyperimmune rabbit antiserums for testing.[34] When an Adenovirus that is unclassified is found to be serologically distinct from all existing types, it is placed as a new specific viral type. At present, by utilizing the neutralization test, 12 distinct Adenovirus types have been established from human sources and two from simian materials.[34, 41] In addition, several other Adenovirus strains are known which have not been placed in present classification of 14 serological types. These strains await completion of reciprocal neutralizing antibody titrations before their qualifications as additional serotypes can be evaluated.

There are other properties of the Adenoviruses which can be demonstrated in the laboratory. These viruses are resistant to ether, sulfonamides, and antibiotics, but they are destroyed by heating for 30 minutes at 56 degrees Centigrade. They are non-pathogenic for all laboratory animals studied (mice, guinea pigs, and rabbits), using several routes for inoculation of the animals with the viruses.[26, 37]

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. An important characteristic of these viruses is their exhibition of cytopathogenicity. This capacity to injure or destroy susceptible cells in which they are multiplying is not unique to the Adenovirus group, but is seen in many viral species growing in tissue culture. The presence of viral agents, therefore, can be determined by a more rapid and convenient manner than by using laboratory animals. In addition, the infectivity of virus suspensions and identification of their specific antibodies can be measured by the amount of cell degeneration caused by the virus.[13]

Observation of this trait of cytopathogenicity in uninoculated cultures of adenoid tissue by Rowe and associates[36] resulted in the isolation of agents of the Adenovirus group. Since that time, a large number of Adenovirus strains have been isolated in tissue cultures of various human and monkey tissues by a number of workers, from a variety of clinical respiratory syndromes.[33]

In studying the cytopathogenicity of these respiratory viruses, the HeLa carcinoma cell cultures, trypsinized monkey kidney cultures, and explant cultures of human embryo epithelium have generally been used. The HeLa cells are particularly sensitive to the injurious effects of these viruses. Focal areas of injured cells appear in the culture tube, usually at the periphery of the tissue cell sheet. As the cell changes spread toward the center of the sheet, the cells round-up and fuse into highly refractile clumps which peel off the glass tube and float in the culture fluid. The injured cells are granular in appearance and lacking in outline, and many exhibit densely staining nuclei.[13]

Harford and associates[19] studied cytopathogenic effects of the Adenoviruses on HeLa cells by electron microscopy. They noted that the cytoplasm of the infected cells contained increased numbers of dense osmophilic granules composed mainly of lipid which they considered to be products of mitochondrial degeneration. The nuclear changes revealed numerous clusters of virus-like particles in the infected cells. These particles were small and somewhat ovoid in shape (30 x 50 microns). They were usually arranged in rows within a cluster, suggesting crystal formation.

Dingle and his co-workers[12] made some interesting observations concerning the characteristics in tissue culture of one member of the Adenovirus group (designated formerly as AD Type 3 virus). It was noted by these investigators that the virus was adsorbed to the HeLa cells at a relatively slow rate and did not spread readily from infected to non-infected cells. Also, their experiments demonstrated that only a small percentage of the viral agent was liberated from the cells in which it propagated. They postulated that these properties of inefficient adsorption and poor dissociation of the viruses might explain the limited spread of this agent to susceptible hosts.

They also found that infected HeLa cells would continue to carry out active metabolism even though supporting viral multiplication. These cells continued to utilize glucose even with marked pathologic changes observable. The viral-infected tissue culture tubes showed increased acidity as compared to the non-infected tubes. Thus, infection with the virus would institute marked cytopathologic effect but apparently did not result in cell death. This finding is compatible with the clinical picture of a self-limited disease produced by the viral agent.

Epidemiology

The original epidemiological studies, performed in connection with the diseases caused by the Adenoviruses, were undertaken by the Commission on Acute Respiratory Diseases during World War II. The work of the commision with the entity termed ARD, later shown to be caused by Adenovirus Types 4 and 7, laid the groundwork for the rapid acquisition of knowledge about this new group of viruses, once isolation of the agents had begun.

The Type 3 Adenovirus, the causative agent of pharyngoconjunctival fever, has been extensively studied from an epidemiological standpoint. The original investigators[4] who named the disease reported that there was an incubation period of five to six days preceding the onset of illness. During the first few days the illness is highly communicable, but this decreases to practically nil after the ninth day.

The true prevalence of the disease is unknown. This clinical entity occurs in localized epidemic and sporadic form in all age groups (mostly children) and in both sexes. Bell et al. felt that carriers were not an important source of infection. They also suspected that contaminated swimming pools might be a source of infection for pharyngoconjunctival fever.

Further investigation by other workers[7, 30] has helped to find the role of the swimming pool in transmission of this disease. Cockburn[6] described an epidemic of conjunctivitis associated with pharyngitis, cervical lymphadenopathy, fever, and myalgia, which occurred in Greeley, Colorado, in the summer of 1951. No etiologic agent was discovered at that time. A history of swimming in the local pool, or direct contact with someone who had been swimming there, was obtainable in most cases. The attack rate among swimmers was estimated to be 25 to 50 per cent. Using paired sera that had been stored

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from the 1951 Greeley outbreak, Cockburn and associates[7] were able to determine by serological testing that Type 3 Adenovirus was apparently the causative agent in the epidemic. The clinical features of the cases in the Greeley epidemic closely resembled those described in 1955 for pharyngoconjunctival fever.

Other outbreaks of this disease occurred in Washington, D. C., in 1954 and in Toronto, Canada, in 1955. The swimming pool was also implicated in these epidemics. The Canadian city's outbreak, as reported by Ormsby and Aitchison,[30] followed the pattern of the one in Greeley. The onset of symptoms occurred within 6 to 10 days after swimming in the city's pools. The disease was transmitted, in many cases, by direct contact with other persons. In some families all persons developed the disease, including the parents. The Type 3 virus was isolated in this epidemic also.

An interesting epidemiological study was performed by Ward and his co-workers in 1955.[39] They inoculated a group of young male volunteers, ages 21 to 25, on the conjunctiva of one eye and on the posterior pharynx, using either Type 3 or 4 Adenovirus. These workers found that illness indistinguishable from pharyngoconjunctival fever was produced in the volunteers. Racial differences among the men apparently did not affect the clinical response.

Additional studies of Adenoviruses in volunteers were carried out by Bell and others.[2] Using Types 1, 2, 3, 4, 5, or 6 for intranasal instillation, and Type 4 virus for swabbing of the oropharynx, the investigators were able to produce infection, as demonstrated by complement-fixing antibody response. Both infection and illness were produced in volunteers by swabbing the conjunctiva with Adenovirus Types 1, 3, 4, or 5. Volunteers developed a moderately severe self-limited, catarrhal conjunctivitis associated with systemic symptoms similar to those of pharyngoconjunctival fever.

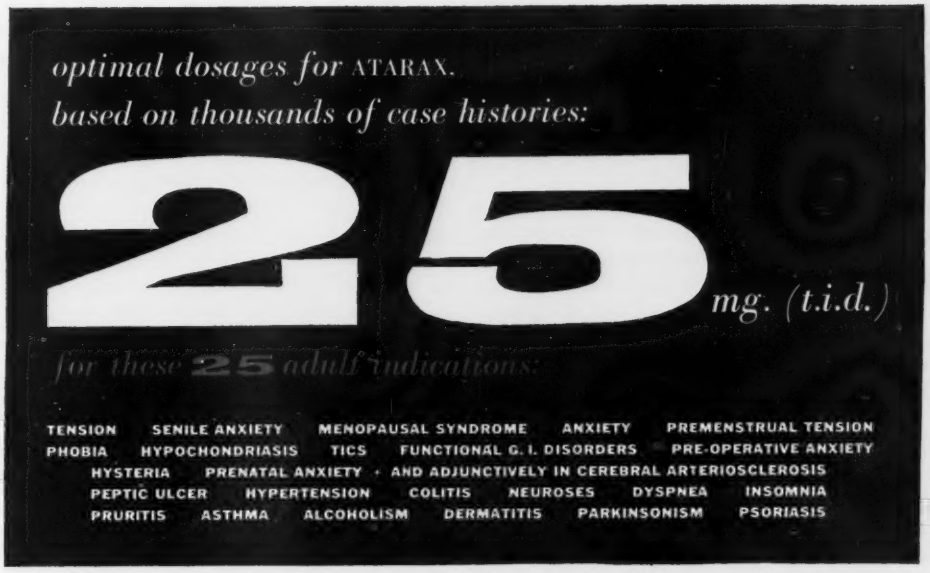
Infection with Adenovirus Type 4 (prototype RI-67) constitutes a problem of considerable importance among new recruits in the armed forces. In some epidemics, as many as one-third of the recruit population has been hospitalized during the winter months with the ARD syndrome. Second outbreaks did not occur in the involved units, so immunity seemed to follow the infection.[9] In one study reported by Hilleman and associates[23] of an epidemic at Fort Dix, New Jersey, in the winter of 1954, there was a significant rise in antibody titer to the RI-67 virus in over 75 per cent of the new men, during the first eight weeks. These workers felt that a reservoir of infection was present in the human population, with possible activation of latent virus from healthy persons. Infection with the Type 4 agent most commonly occurs during the middle years of life, with the highest incidence between ages 18 and 25, according to one study.[21]

Adenovirus infections in the civilian population are common, as determined by serological studies on various age groups. There is serologic evidence that one-third of the population may acquire infection with the Type 6 Adenovirus before age 45 is reached.[26] In the study by Gnesh and others[18] on random blood specimens, it was found that antibodies to the Adenovirus group were present in high titer, and prevalent in a large percentage of the sera tested. It is unknown, as yet, whether the majority of persons undergo the infection during epidemic spread of the virus, or whether its endemic presence results in sporadic infections leading to type-specific immunity.[27]

Although much of the epidemiological study of the Type 4 Adenovirus (RI-67) was performed in the armed forces, there have been studies with the civilian population. One of the most interesting of such studies related to the inoculation of 14 volunteer adult patients suffering from advanced cancer.[38] These patients were inoculated by the respiratory route (nine of the patients) or parenterally. This experiment was performed in 1954, and it was one of the early attempts to transmit the RI-67 agent to produce disease in the recipient. The investigators found that neutralization and complement fixation antibody appeared or increased in amount in all inoculated patients who survived for at least nine days after injection. None of the volunteers developed significant illness, however. They observed no convincing evidence of cancer regression or selective localization of the virus in the cancer tissue.

A group of investigators attempted to determine the prevalence of respiratory infections produced by the RI-67 agent in a large city, using serologic testing for the epidemiological work. They found that the RI-67 virus (Type 4 Adenovirus) had apparently not produced many of the respiratory infections in that city. Instead, another viral agent which they termed the JL virus seemed to have been associated with the syndromes classified as ARD and non-streptococcal pharyngitis. Immunologically, this JL agent was determined to belong to the Type 3 Adenovirus group.

Balducci et al.[1] performed epidemiological studies in England during 1954 and 1955 to determine the presence of Adenovirus infection in that country. They found that complement-fixing and neutralizing antibodies against the Adenoviruses were widely distributed in sera collected in northern England. These workers also were successful in isolating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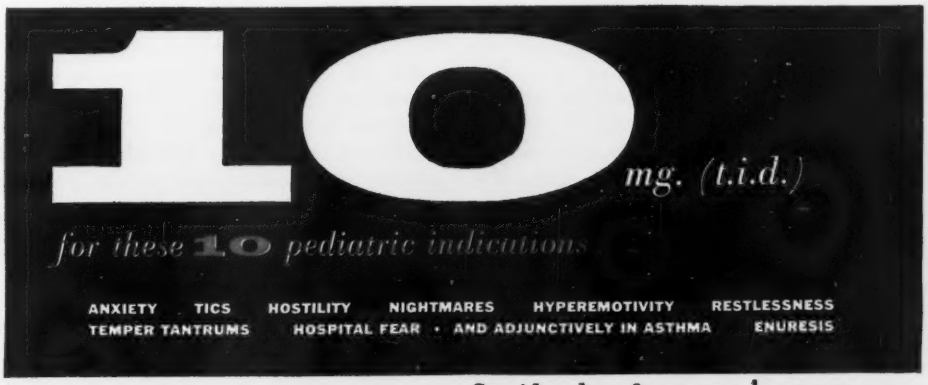
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viruses from human adenoid tissue and identifying these agents as members of the Adenovirus group. Their work also confirmed American studies as to the prevalence of the complement fixing antibodies and the age at which they are found. They did not find the high incidence of infection of soldiers that Hilleman found in United States military personnel.

Treatment and Prevention

Little success has attended the search for drugs or other measures that will cure viral diseases, such as those caused by the Adenovirus group. Ryan, O'Rourke, and Iser[37] found no clinical or tissue culture response to the known antibiotics or sulfonamides, by the agent of pharyngoconjunctival fever. However, they did obtain a rapid abatement of signs and symptoms in most patients by using a combination of topical corticosteroid and antibiotics or sulfas. They noted no exacerbation of the disease with cortisone therapy.

Likewise, Dascomb and Hilleman[8] found that Terramycin did not influence the disease course produced by infection with an agent of the Adenovirus group. Symptomatic therapy for their patients included steam inhalation and analgesic doses of codeine, to reduce cough intensity. In addition, bedrest, aspirin, and adequate intake of fluid were advised. These workers also suggested that local anesthetics and opiates might be of benefit, although they did not use these in their patient study.

Dingle[9] suggests that selective passive immunization of new recruits with human gamma globulin might help prevent or reduce epidemics which result in the loss of numerous man-days of training in the military forces.

The greatest potentiality for prevention of such epidemics, however, is through the avenue of active immunization. To this end, Adenovirus vaccines have been prepared and studied in volunteers. The first such study was reported by Bell, Huebner, and their group of investigators at the National Institutes of Health.[2, 25] They prepared heat-inactivated and formaldehyde-inactivated vaccines against Type 3 Adenovirus, using a viral strain that had originally been isolated from a patient with pharyngoconjunctival fever. A total of 45 persons received intramuscular inoculations of either of the prepared vaccines. Of those inoculated, 78 per cent showed the development of Type 3 neutralizing antibodies, and no untoward reactions occurred. The volunteers were challenged with the Type 3 Adenovirus by swabbing the palpebral conjunctiva of one eye with the virus.

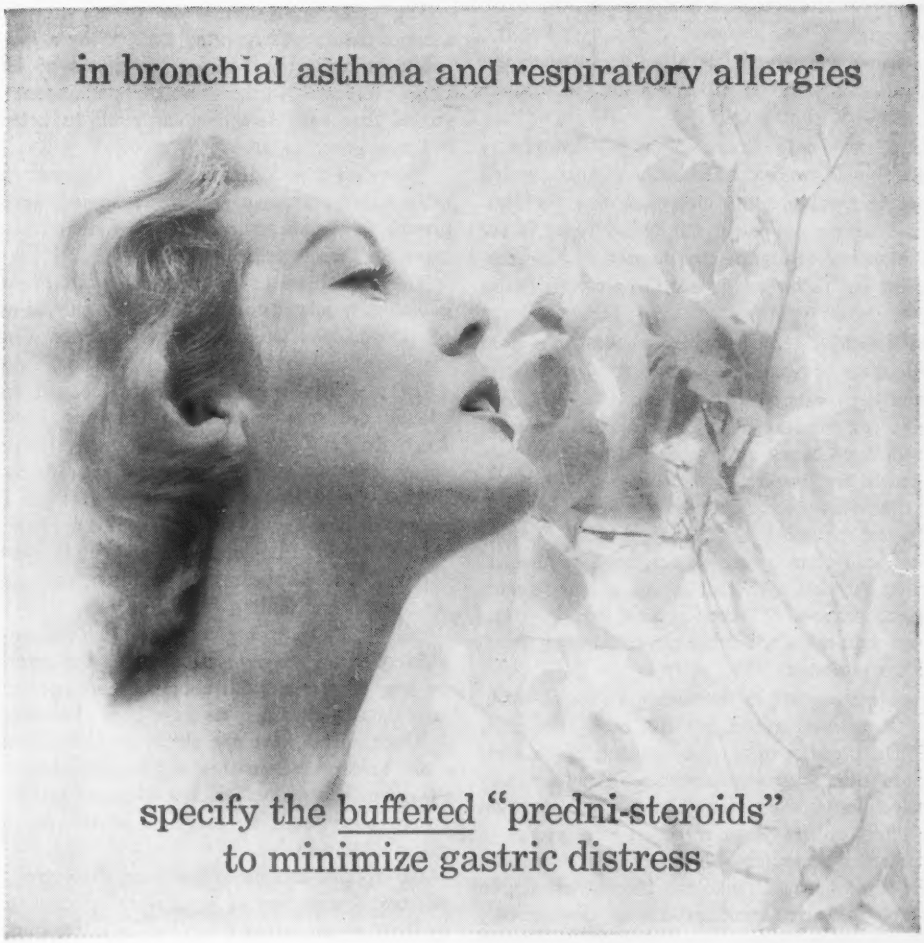
Observers in this study found that volunteers with vaccine-induced antibodies experienced greater protection against illness and infection than did vaccinated or unvaccinated persons without demonstrable antibodies. The vaccine-induced protection apparently was equal to the unvaccinated volunteers' protection from naturally acquired antibodies.

The report of a field trial with a new Adenovirus vaccine was announced in 1956 by the Public Health Service and the Navy Department.[3, 43] The study was performed on naval recruits at the Great Lakes Naval Training Center, utilizing a trivalent Adenovirus vaccine of Types 3, 4, and 7. A single 2 cc. injection of the formaldehyde-inactivated vaccine was given intramuscularly to 4,000 naval recruits at the base early in 1955. Although the findings were incomplete, the preliminary results did show that a neutralizing antibody response occurred to each of the three virus types in the vaccine, and that no untoward local or general reactions were manifest. The workers felt that 50 to 70 per cent of the total expected febrile respiratory illnesses were prevented by the vaccine. During the period of observation, illness due to Types 3 and 7 Adenovirus was not prevalent, but the Type 4 virus was encountered in a substantial proportion of these feverish respiratory illnesses. All evidence indicated that the vaccine induced a definite reduction in the rate of occurrence of illnesses associated with Adenovirus Type 4. It was postulated by the investigators that "vaccination of substantial numbers of arriving recruits might produce herd immunity sufficient to completely prevent outbreaks among recruits of respiratory illness due to the Adenoviruses, preventing the usual interference with military training routine."[3]

Discussion

As one considers the important role played by various respiratory infections in the total spectrum of human diseases, it is readily apparent that any progress in this field has valuable implications. The problem of the common cold, with its great economic and medical effects upon the human population, demonstrates the necessity for continuing research for the etiology, pathogenesis, and therapy of many of these infectious diseases of the respiratory tract. The discovery of the Adenovirus group, and the subsequent incrimination of these agents as the cause of certain respiratory illnesses of previously unknown etiology, portend future similar results of research for other agents which cause these infections. Thus, the stimulus supplied by research with Adenoviruses may yield better elucidation of the whole problem of respiratory infections in man.

Although the difficulty of terminology has been clarified to a large degree by recent agreement of interested workers to use the name Adenovirus group for the newly-discovered agents, the final word has



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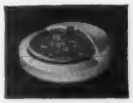

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not been stated in this matter. The ultimate name must be approved by the Subcommittee on Viruses of the International Nomenclature Committee, but the present name has served, at least, to eliminate the great confusion of terms previously seen in medical literature.

Isolation of more strains of the Adenoviruses undoubtedly will continue. Separation of these strains into specific types presents somewhat of a problem. The total number of these serological types is yet to be determined, using the classification of Huebner, since many strains do not fit into the presently-designated 14 specific types.

Most isolations of Adenoviruses have come from adenoid tissue or secretions of the respiratory tract and from the conjunctiva of the eye. However, in a few instances, viral agents of this group have been recovered from feces and other organs not associated with the respiratory tract.[8, 13] Investigators found the viruses in a case of mesenteric lymphadenitis, in the stool of an infant with Roseola infantum, and from a case of Letterer-Siwe disease. This raises the possibility that certain of these agents may cause diseases of other organs, besides those of the respiratory tract. Further research in that direction seems indicated.

A problem relating to the common sites of infection by these viral agents has not been adequately solved. The presence of several antigenic Adenovirus types in tonsillar and adenoid tissue, without evidence of production of overt disease, raises the question of the effect of this silent infection if it proves to be of marked chronicity. Enders[13] has speculated that the viruses may act like the Herpes virus, with the latent infective agent producing disease only under appropriate stimuli. Also, the relationship of long-standing silent infection to tonsillar and adenoid hypertrophy has not been explained completely.

Successful results presented in preliminary reports of a field trial with a new trivalent Adenovirus vaccine are encouraging for their promise of preventing respiratory illnesses caused by the Adenovirus group. This vaccine used only Types 3, 4, and 7, but it was apparently effective against these types. Undoubtedly, a vaccine could be produced that would combine all specific types of the group that have been shown to produce clinical disease. Utilization of such a vaccine would have great value in prevention of large-scale epidemics that have occurred in the military population and in some civilian groups. A major portion of future research with the Adenovirus group probably will be devoted to the preventive medicine aspect, through the method of active immunization.

Summary

The isolation of a new group of viruses from adenoid tissues was reported in 1953 by a group of investigators at the National Institutes of Health. Other research workers isolated additional viral strains that were later demonstrated to belong to this new group of agents.

Following a period of confusion in nomenclature, interested workers in this field agreed upon the present term "adenovirus group" for the collective name for these agents.

The Adenoviruses have been discovered to be etiologically related to several distinct clinical entities of previously-undetermined cause. Types 4 and 7 are associated with "acute respiratory disease" (ARD), while Type 8 has been isolated from a specific eye infection termed epidemic keratoconjunctivitis (EKC). Pharyngoconjunctival fever is apparently produced by infection with Adenovirus Type 3. Common clinical features present in illness produced by these viruses include fever, pharyngitis, cervical lymphadenopathy, and respiratory symptoms of cough and hoarseness. In addition, conjunctivitis is a prominent finding in many cases.

All agents in this group share a common complement-fixing antigen. Specific types are determined by use of the neutralization test. At present, 14 serologically distinct types have been classified.

These agents have the ability to grow in various tissue cultures where they exhibit the characteristic of cytopathogenicity. Nuclear changes produced in tissue culture cells by members of the Adenovirus group are distinctive.

No specific treatment has been discovered to be effective. Prevention of respiratory infections caused by these agents, using a vaccine for active immunization against the viruses, may be the method for control of such diseases. Production of a trivalent vaccine, and recent testing of this vaccine in a field trial, have demonstrated the effectiveness of such a measure for developing an active immunity to the Adenoviruses.

Through the intensive efforts of several different groups of investigators, the solution to the problem of at least some of the many respiratory infections may eventually result.

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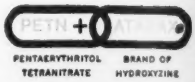

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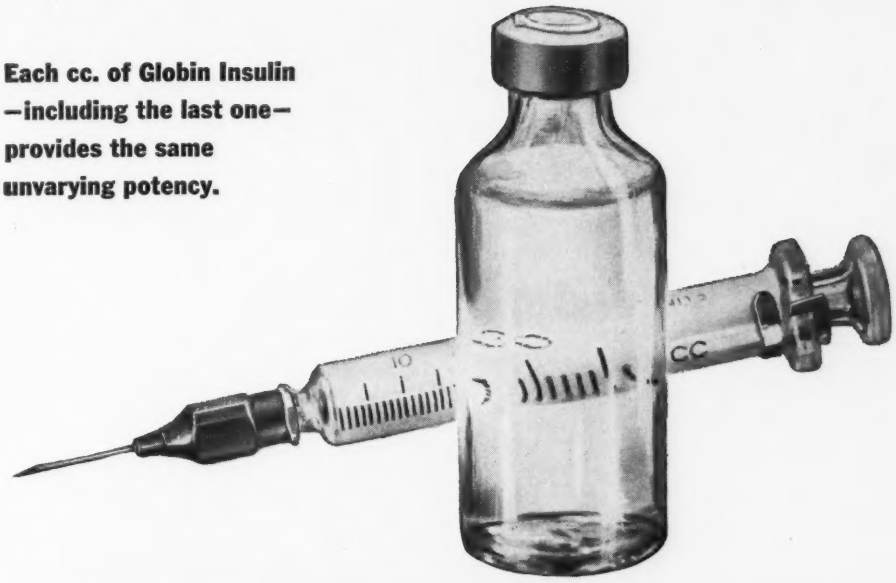

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DEATH NOTICES

Alonzo Pitt Gearhart, M.D.

Dr. A. P. Gearhart, 84, who had practiced in Wichita for 30 years before his retirement in 1951, died at his home in Oceanside, California, on August 18. He was an honorary member of the Sedgwick County Medical Society and a fellow of the American College of Surgeons. Dr. Gearhart was graduated from the University Medical College of Kansas City in 1898 and practiced first in Blackwell, Oklahoma, moving to Wichita in 1921.

Henry Blackburn Miller, M.D.

Dr. H. B. Miller, 76, Shawnee County physician since 1909, practicing principally in Rossville, died at a Topeka Hospital on September 8. For a short while in his youth he was a chemistry instructor at the University of Kansas, but he later studied at the University of Pennsylvania School of Medicine, graduating in 1908. The next year he joined his father in practice in Rossville.

Clarence Avery Parker, M.D.

Dr. C. A. Parker, 80, an honorary member of the Sedgwick County Medical Society, died at his home in Wichita on September 19 after an illness of four months. A graduate of the University of Nashville College of Medicine in 1903, Dr. Parker began practice in Maize, remaining there until he was called to serve in the medical corps during World War I. He had practiced in Wichita since 1922.

George Arthur Westfall, Sr., M.D.

A member of the staff of the Hertzler Clinic, Halstead, for 27 years and a former chief of staff there, Dr. G. A. Westfall, 66, died at a Halstead hospital on September 18 after an extended illness. He was an honorary member of the Harvey County Medical Society. Dr. Westfall, a fellow of the American College of Physicians, was graduated from Tulane University School of Medicine in 1913 and began practice in Kansas in 1918. Two of his sons are physicians and one, Dr. G. A. Westfall, Jr., practices in Halstead.

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tracheitis
ethmoiditis
streptococcal pharyngitis
nasopharyngitis
tracheobronchitis
bacterial pneumonia due to resistant pneumococci, staphylococci, or mixed flora
viral or nonspecific pneumonia not responsive to other therapy
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38 patients had fair response

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and with outstanding safety and toleration **914** patients had no side effects

References: 1. Case reports in the Pfizer Medical Department Files from fifty-three clinicians, and the following published reports: Shubin, H.: Antibiotic Med. & Clin. Therapy 4:174 (March) 1957. Carter, C. H., and Maley, M. C.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 51. Winton, S. S., and Chesrow, E.: Ibid., p. 55. LaCaille, R. A., and Prigot, A.: Ibid., p. 19.

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Increasing use of Signemycin V and other Signemycin formulations has confirmed the value of this agent in the armamentarium of the physician treating antibiotic-susceptible infections, particularly those seen at home or in office where susceptibility testing may not be practicable and where immediate institution of the most broadly effective therapy is necessary.

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Increase in Hospital Usage

The ratio of hospital admissions to population in the continental United States outstepped the total population increase in the 11-year period 1946-1956, according to the annual report on hospital statistics published recently in the *Journal of the American Hospital Association.*

Admissions to hospitals of all types in 1956 were 22,089,719, or 132 per thousand population. In 1946 the rate was 112 per thousand population. Had the ratio of admissions to population remained constant at the 1946 level, there would have been only 19 million admissions in 1956, rather than the actual 22 million reported. Over the 11-year period, the number of admissions climbed 41 per cent, and from 1955 to 1956, nearly 5 per cent.

The hospital statistics released today were compiled from questionnaires sent to 6,966 hospitals listed by the American Hospital Association in its annual directory of hospitals. These statistics cover the years from 1946, when the Association began its statistical series, through 1956.

The 6,966 hospitals in the continental United States had 1,607,692 beds and an average daily census of 1,355,792 in 1956. Of these hospitals, 51 per cent were nonprofit, 17 per cent proprietary, 6 per cent federal and 26 per cent state and local governmental hospitals.

The voluntary nonprofit hospitals led in number of admissions—nearly 15 million in 1956. Over 4 million admissions were to state and local governmental hospitals. Proprietary and federal hospitals each accounted for about 1.5 million admissions.

Of the average 1,355,792 patients in hospitals on any given day in 1956, 62 per cent were in state and local governmental hospitals, 24 per cent in nonprofit hospitals, 12 per cent in federal hospitals, and 2 per cent in proprietary hospitals. The large percentage of patients in the governmental hospitals each day reflected a high proportion of psychiatric and tuberculosis institutions providing predominantly long-term care.

Although less than 2 per cent of all admissions were to psychiatric hospitals in 1956, 53 per cent of all patients in hospitals on any given day were in psychiatric institutions.

The number of hospital births reported in 1956 was 3,491,141, an increase of 64 per cent over 1946 but only 1 per cent above the 1955 figure. Nearly 72 per cent of the total hospital births in 1956 were in short-term nonprofit hospitals, while 18 per cent were in nonfederal governmental hospitals, almost 6 per cent in proprietary hospitals and 4.5 per cent in federal hospitals, the Association's statistics showed.

Total hospital assets, first reported in 1947, rose in 10 years from less than $6 billion to more than $13 billion for all hospitals, an overall jump of 122 per cent and a rise of 9 per cent from 1955 to 1956. At the same time, the total expenditure by hospitals for the care of patients passed the $6 billion mark in 1956, an increase of 207 per cent in 11 years and nearly 8 per cent in the last year. Payroll expense for all hospitals was almost $4 billion in 1956, an increase of 258 per cent in 11 years and a jump from 56 per cent of the total hospital expense in 1946 to 66 per cent in 1956, according to the Association.

Assets for the 3,165 nonprofit short-term hospitals in the continental United States totaled almost $6 billion. These hospitals spent almost $3 billion for patient care in 1956, a rise of 223 per cent from 1946 to 1956, and 9 per cent in the last year. Payroll expense was almost $2 billion.

Length of stay in short-term general and special hospitals, which had dropped from 9.1 to 7.8 days from 1946 to 1955, went down .1 day to 7.7 days in 1956, with a decrease from 9.7 to 9.4 days in nonfederal governmental hospitals. Length of stay in nonprofit short-term hospitals was 7.5 days, and in proprietary hospitals 5.6 days, unchanged for both these types from 1955 to 1956, the Association reported.

Nonprofit short-term hospitals in 1956 spent $24.99 per day to care for each patient, an increase of 149 per cent from the 1946 figure of $10.04. The rise from the 1955 level of $24.15 was a little over 3 per cent.

The cost to the nonprofit short-term hospitals for the average patient stay rose less than the hospital's cost per patient day during the 11-year period, because of the reduction in length of stay. From 1946 to 1956, the average cost to the hospital per patient stay rose from $88.35 to $187.43, an increase of 112 per cent as compared with the 149 per cent increase in the hospital's expense per patient day. Since length of stay remained unchanged from 1955 to 1956 in short-term nonprofit hospitals, the increase in cost both per day and per stay from 1955 to 1956 was about 3 per cent, the Association said.

Full-time personnel employed by all hospitals totaled 1,374,704 in 1956, an increase of 66 per cent in 11 years and nearly 6 per cent in the last year of the period.

In all hospitals in 1956, there were an average of 101 personnel per 100 patients, an increase of 28 people per 100 patients in 11 years. Short-term nonprofit hospitals had 213 personnel per 100 patients in 1956, while at the other extreme, nonfederal psychiatric hospitals had 31, the Association's statistical survey revealed.

Worry affects the circulation, the heart, the glands, the whole nervous system, and profoundly affects the health. I have never known a man who died from overwork, but many who died from doubt.—*Charles Mayo, M.D.*

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BOOK REVIEWS

Clinical Proctology. Second Edition. By J. Peerman Nesselrod, M.D. Published by W. B. Saunders Company, Philadelphia. 296 pages, 72 figures. Price $7.00.

Dr. Nesselrod's concise style is again noted in this second edition of his very popular work. The basic material is briefly and practically presented. The chapter on anal infection clarifies the etiology of most common anorectal pathologies and rationalizes their treatment. Anal infection is further elaborated upon in each subject-chapter in which it is pertinent. Examination, pre-and post-operative management, therapy, and operative methods are those of the author.

Other chapters include anorectal malformation; clinical proctoscopy; neoplastic diseases, and miscellaneous subjects—all are brief but adequate. This is not an encyclopedic work but a clear, concise work which is easily read and understood. Dr. Nesselrod gives the reader the method he has found most satisfactory after years of experience as a clinician and teacher of proctology in a large medical center. The book is recommended for every physician as a ready source of knowledge in an area subject to frequent organic changes.—*L.A.S.*

Orthopedic Surgery in the Mediterranean Theatre of Operations. Part of Official History of Medical Department of U. S. Army in World War II. Edited by Col. John Boyd Coates, MC; Mather Cleveland, M.D., and Elizabeth M. McFetridge, M.A., Office of Surgeon General. 368 pages. Price $4.00.

This is a history of the development and employment of military orthopedic surgery in World War II. It is one of a series of volumes published under the auspices of the Medical Department of the United States Army. The book is not large (340 pages), but it contains numerous photographs and illustrations that illuminate each major point. The following examples will illustrate best the scope of the book.

The events and decisions that led inevitably to final definition of treatment principles to be applied in handling the wounded soldier are reviewed from the over-all medical standpoint. The medical plan as it finally evolved was not assembly line medicine with a physician at each medical station performing one assembly line performance in the chain of evacuation, but more aptly might be compared to a conveyer belt from the Battalion Aid Station to the general hospital. The conveyer belt progress could be interrupted at any point and the wounded soldier held for definitive treatment or, if recovered, he could be returned to combat.

Initial surgery was of necessity in the Combat Zone, reparative surgery in the Communications Zone, and reconstructive surgery in the Zone of the Interior. The tale of the development of this plan by blood, discouragement, and experience will be especially interesting for those officers who served through the Mediterranean campaign.

It is worth pausing to recall the impact penicillin had on the morbidity and mortality of the wounded. Penicillin was a major factor in permitting the change in compound fracture treatment from the ritualistic Carrel-Dakin treatment of World War I of cleanse, debride, irrigate, drain, and immobilize to the World War II policy of cleanse, debride, close, and mobilize. This medical advance resulted in the preservation of the military usefulness of thousands of soldiers.

The evolution and function of the highly efficient medical consultant system is also described in detail. Now that a lapse of years permits a more objective analysis of the whole medical personnel structure with their varied training and capacities, it may be seen that the medical consultant system was a most essential step. The consultant was the medical liaison officer who disseminated by personal visits new techniques, corrected faulty procedures, and welded the Medical Corps into one cohesive unit.

To Oscar Hampton, the author, medicine owes a sincere vote of thanks for his excellent treatment of a difficult subject and the preservation of the story of the anguished development of military orthopedic medicine in World War II.—*H.O.M.*

Modern Therapy in Neurology. Edited by Francis M. Forster, M.D. Published by C. V. Mosby Company, St. Louis, Missouri. 792 pages. Price $12.00.

For too long now the field of neurology has been represented as one of diagnostic and research potential alone. Too little stress in the training of the young neurologist has been placed upon his *role in the treatment* of illness affecting the nervous system. It is, therefore, refreshing and encouraging to have available this treatise on modern therapy in neurology.

Experienced and respected neurologists have collaborated to present in readable fashion the traditional method of treatment of familiar neurologic disorders. It might be said that too many pages are devoted to diseases and treatment situations in which neurologists at large possess no special talents either by training or experience; or that some chapters more suggest sifting of recent literature than opinions of experienced therapists.

But this book is obviously not a manual of helpful hints or special tricks in treatment of specific neurologic patients; it is rather a talented display of the broad scope of usefulness of the trained neurologist in the treatment of illness, and in this light it is a magnificent success.—*J.A.S.*

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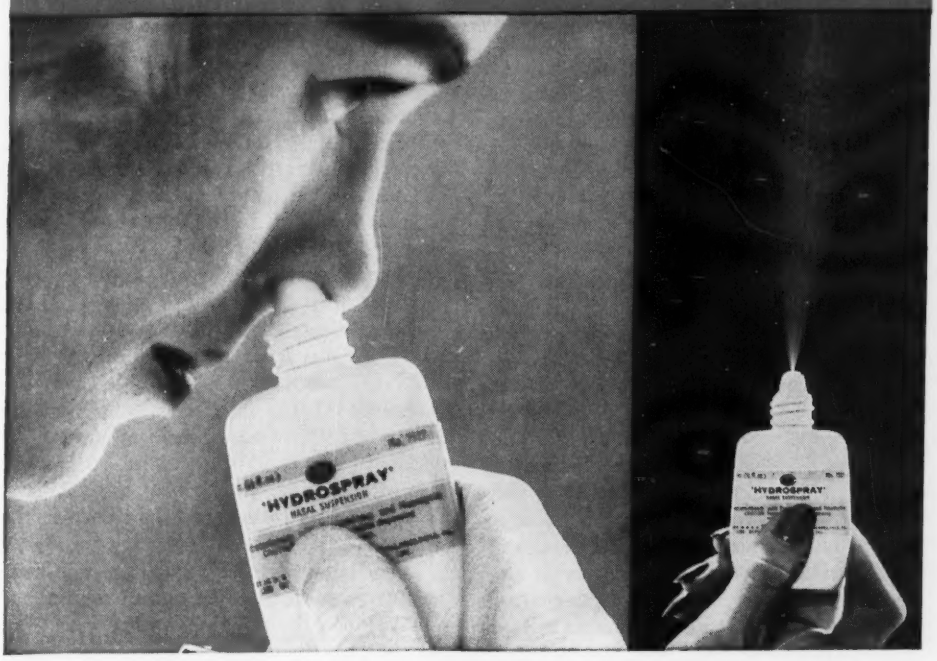

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REFERENCE: 1. Silcox, L. E., *A.M.A. Arch. Otolaryng.* 60:431, Oct. 1954.

Psychosomatic Medicine: A Clinical Study of Psychophysiologic Reactions. Third Edition. By Edward Weiss, M.D., and O. Spurgeon English, M.D. Published by W. B. Saunders Company, Philadelphia, 557 pages. Price $10.50.

This useful and important book has undergone extensive revision of material and a general reorganization which is most welcome inasmuch as a great mass of data has accumulated since the publication of the second edition in 1949. The senior author's background and original training in pathology have proved to be almost invaluable in enabling him to sort out important contributions and present them in such an objective manner. This has resulted in a work that is practical, concise, and easily readable, and it still contains sufficient theoretical background material to support important data.

This book is ideally suited for the use of the clinician. It contains very little material that could not properly be incorporated into a volume on internal medicine, but until such time as there is better integration between the emotional and somatic considerations of disease, the clinician could well consider this book a supplement to his books on internal medicine and physiology.

The book is organized in two parts. The first part consists of 176 pages devoted to the general aspects of psychosomatic medicine. The chapters on "Personality Development and Psychopathology" and "Everyday Problems of Psychotherapy" are well worth the time of any clinician. The second portion of the book, "Special Applications to General Medicine and the Specialties," consisting of 347 pages, is an excellent discussion particularly applicable to those clinical problems in which illness is partly dependent on emotional factors and those cases in which the vegetative nervous system is definitely involved in the production of the disease and secondary pathological changes.

Although the authors do not state it in so many words, it is obvious that it is their feeling that in many cases it is desirable that the clinician not only have a thorough understanding of the underlying psychological factors, but also that he can find a great deal to do in the area of psychotherapy. This book is evidently an attempt to help the clinician have a better understanding of these underlying factors, a better understanding of his important role in psychotherapy, to give him reassurance in making that all-important decision as to whether he is capable of going ahead with the patient or whether specialized psychiatric help should be sought. Very little space is devoted to the strictly psychiatric problem that is best cared for by the psychiatrist. This is in no sense a textbook of psychiatry, but one that could well have its place in any general medical library.—*T.L.F.*

The Treatment of Burns. By Curtis P. Artz, M.D., and Eric Reiss, M.D. Published by W. B. Saunders Company, Philadelphia. 250 pages, 199 illustrations on 105 figures. Price $7.50.

This is a practical handbook for the doctor dealing with burned patients. Emphasis is placed on the multiplicity of pathologic changes in the severely burned patient, as well as on rational treatment. From accumulated information from the literature, and from careful observations in the treatment of more than 1,000 burned patients over a period of seven years at the Brooke Army Medical Center, the authors present an integrated regimen for treatment. The magnitude of the burn problem, both civilian and military, and the general need for more expert treatment on the part of the practitioner are stressed.

General immediate care depends on: (1) estimation of percentage of body surface burned; (2) estimation of depth of burn; (3) evaluation of site of burn; (4) evaluation of age and physical condition of the patient. From the above observations, patients are classed into critical, moderate, and minor cases.

The critical cases include: (1) burns with injury to the respiratory tract; (2) partial thickness burns of more than 30 per cent of the body surface; (3) full thickness burns of face, hands, feet, genitalia, or more than 10 per cent of the body surface; (4) burns complicated by fractures or soft tissue injuries; (5) electrical burns; (6) deep acid burns.

These patients should be sent to a well equipped general hospital and placed under the care of experienced clinicians.

Moderate burns include: (1) partial thickness burns 15 to 30 per cent of the body surface; (2) full thickness burns of less than 10 per cent of body surface provided face, hands, feet, or genitalia are not involved. These patients may be treated in the community hospital.

Minor burns include: (1) partial thickness burns involving less than 15 per cent of the body surface, and (2) deep burns involving less than 2 per cent body surface. These may be treated as out-patients and hospitalized for skin grafts, when necessary.

Aside from the obvious immediate care for the patient, the following outline of immediate organized procedures is suggested: (1) history—overall estimate of burn, weight of patient; (2) determine need for tracheotomy; (3) reassure patient, give intravenous morphine; (4) draw blood for laboratory determinations and start fluids; (5) if necessary, insert cut-down canula; (6) insert indwelling catheter into bladder; (7) plan fluid therapy; (8) give antibiotics; (9) give tetanus antitoxin or toxoid; (10) give local care; (11) make work sheet-type chart.

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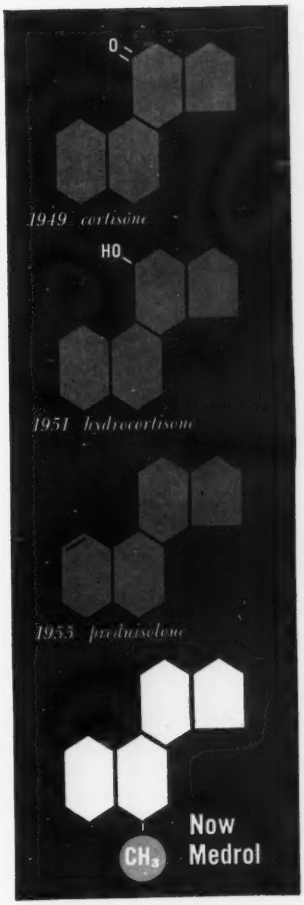

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loss of liquid, mineral, and protein elements. The Brooke modification of the Evans formula for fluid replacement is presented. Provision for individualization of the patient should be made. Local care of burned areas is somewhat dependent on location, extent, and degree of the burn. Generally the aim is to secure earliest coverage with minimal complications. Relative merits of occlusive and exposure treatment are discussed.

General and specific problems of reconstruction are mentioned. Early removal of eschar of the face is rarely indicated. A tracheotomy should be done on severe burns of the face. Eyelids should be grafted early if there is danger from corneal ulceration. Hands and other joint surfaces should be covered early. The penis should be grafted early, whereas the perineum may be allowed to granulate pending coverage of other areas.

Under "Metabolic Response and Nutrition," nitrogen balance, fat loss, fluid and mineral changes, endocrine variations, and vitamin needs are discussed. Detailed management includes: (1) dietary—caloric needs, specific nutritional requirements, and (2) nondietary—treatment of anemia, multiple transfusions, psychiatric care.

The problem of the debilitated patient is brought to attention. Important laboratory procedures are emphasized.

Practical details of burn therapy include problems of anesthesia, emotional disturbances in the patient, detailed nursing care, and rehabilitation.

In *The Treatment of Burns,* the authors have brought this subject up to date, culling pearls from a vast accumulation of literature and personal experience without being pedantic.—*A.E.H.*

The Specialties in General Practice. Second Edition. By Russell L. Cecil and Howard F. Conn. Published by W. B. Saunders Company, Philadelphia. 780 pages, 76 figures. Price $16.00.

As a textbook for medical students or as a review and reference book for the physician a long time in practice, this book fills a great need. The 15 contributors have carefully selected and chosen the most important and frequently encountered maladies seen in general practice. Then they have carefully presented the least controversial methods of treatment.

Dr. Conn, himself a general practitioner and editor of the *Current Therapy* book so frequently seen on the bookshelf of the general practitioner, has drawn from his experience resulting from both endeavors to produce a ready handbook for the busy practitioner.

The illustrations are plentiful and well selected so that many sketches and photographs are diagnostic and explanatory.

This second edition of a very popular book first published in 1951 has brought the general practice aspects of the contents up to date. All the newer antibiotics, tests, tranquilizers, and psychiatrical attitudes have been included.

Like many books of medicine previously edited by Dr. Cecil, this book will be of real service in the physician's library. It should also serve as a guide in the general curriculum planning of a medical school wherein stress is applied to general practice teaching. —*C.M.B.*

Textbook of Pathology. By Stanley L. Robbins, M.D. Published by W. B. Saunders Company, Philadelphia. 1,351 pages, 933 figures. Price $18.00.

The major part of this book was written by the author with collaborators on only five chapters. The author states that the book is written for students and clinicians and that, among other goals, he has attempted to avoid distracting detail. The detail which may be distracting to the beginning student, however, will be missed by the individual with some knowledge of pathology who wishes additional information. It seems probable that this book will serve its greatest usefulness to the medical student rather than to the clinician. It contains a substantial amount of well presented information, although there are small errors which are difficult to avoid when one author attempts to encompass in his writings a large part of the total field of pathology.

Although the author has placed a considerable emphasis on relating pathology to clinical medicine, this relationship has not been made as clear in some places as might be desired. By intent, the author has selected fewer references than usual and employs them as collateral reading and not as documentary evidence of statements. The parenthetical remarks after references, which serve to assist the potential reader in knowing what he may expect, are certainly helpful. Some physicians, however, will miss the opportunity to be directed to specific articles elaborating on many of the points made in the textbook. In the opinion of this reviewer then, this textbook will not serve many as a ready introduction to the original literature in pathology.

The style of the author's writing is of satisfactory readability and ease of understanding. The use of bold face and italic type is of assistance in emphasizing certain important points. The outlines given at the first of each chapter are helpful in guiding one to the areas of interest within the chapter, some of which are of substantial length and would otherwise

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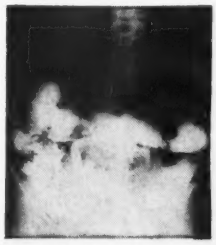

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be quite confusing. Although the printing is generally of excellent caliber, in some copies the bold face type does not stand out distinctly black. The illustrations are generally of outstanding caliber and ample in number.

This textbook should play a useful role by serving as a reasonably thorough introduction to the subject of pathology, being intermediate in length between some of the brief synopses and longer, more detailed books on pathology.—*R.E.S.*

William Harvey: His Life and Times: His Discoveries: His Methods. By Louis Chauvois. Published by Philosophical Library, New York, 263 pages. Price $7.50.

Dr. Chauvois has already been honored several times for his literary work devoted to the history of science and medicine. This volume should add to his laurels. Translated from its original French in the year of its publication, it belongs in the library of every physician who has an interest in the long and rich history of our profession.

The author writes with an authority based on extensive research into the professional and personal life of Harvey, and although one can assume certain details of description to have their origin in the author's imagination, this literary license only serves to make the reading more enjoyable.

Perhaps the outstanding features of this work are the clearly-drawn details of background surrounding the portrait of the man himself. The reader clearly sees Harvey wrestling with the prejudices of his time in civic, political and scientific matters, and always discarding any idea or doctrine which seemed to be based solely on tradition or superstition. His practical approach was instrumental in saving four women who had been condemned as witches.

One also sees Harvey, the skeptical student, Harvey the scientist and physician, and finally Harvey in his last years of retirement, sage and senior citizen whose words and opinions were widely known and revered.

The work is sprinkled liberally with direct quotations and footnotes, the Harvey portraits are reproduced and discussed, and a bibliography of source material is given.—*M.S.A.*

Second Tissue Homotransplantation Conference. Annals of New York Academy of Sciences. Otto v. St. Whitelock, Editor-in-Chief. Volume 64, Article 5, Pages 735-1,073.

This issue contains a compilation of reports of various investigators in the field of homotransplantation of tissues. Emphasis is placed on the use of embryonic, fetal, and neonatal donor tissues. Reports deal chiefly with efforts to beneficially influence the normal host-graft relationship. These progressively pooled efforts and their most fascinating reports, if carried to ultimate success, may eventually open the doors to boundless stores of human "spare parts." —*A.E.H.*

Mental Health Association to Meet

The annual meeting of the Kansas Association for Mental Health will be held in Topeka, October 25 and 26, with headquarters and registration at the Hotel Jayhawk. Three inspirational speakers, five workshops, and tours of the Topeka State Hospital and the Kansas Treatment Center for Children will highlight the program.

Standing committees will meet during the morning of October 25, and the Riley County Association for Mental Health will conduct film previews. Dr. George Jackson, director of institutions for Kansas, will speak at the luncheon session on Friday, and Senator Frank Carlson will give an address at the luncheon meeting on Saturday. Speaker at the Friday evening dinner will be Dr. Seward Hiltner, professor of pastoral theology at the University of Chicago Theological Seminary.

The five workshops will cover chapter organization, educational programs, volunteer services, finances and fund campaigns, and public relations.

Programs and registration blanks may be secured from the association, 324 New England Building, Topeka.

To Study Research and Education

Secretary Folsom of the Department of Health, Education, and Welfare has named a special committee of medical leaders and industrialists to advise him on the "status and future needs" of medical research and education. He asked the members to study such questions as:

1. Impact of expanding research programs on medical education.
2. Availability of scientists, technicians, and facilities.
3. Relative emphasis given to research in the various disease fields.
4. Relative emphasis given to fundamental studies in the basic sciences generally.
5. Relationship between federal and private research programs.
6. Standards for approval of research projects.

The Office of Education reports that for the first time since 1910 the percentage of high school students taking mathematics and science courses is on the increase.

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A.M.A. Plans December Session

Philadelphia will be the scene of the American Medical Association's 11th clinical meeting, December 3-6. Center of activities will be Convention Hall where scientific exhibits, color television, motion pictures, technical exhibits and scientific lectures will be presented. Headquarters for the House of Delegates will be the Bellevue-Stratford Hotel.

Highlights of the three-and-a-half day convention geared especially for the nation's family doctors include: (1) special transatlantic conference between distinguished physicians in London and Philadelphia on "Advances in Chemotherapy of Cancer" via two-way telephone at 3:00 p.m. EST Wednesday; (2) complete color television schedule of surgical demonstrations emanating from Lankenau Hospital; (3) motion picture program daily plus a special session Tuesday evening; (4) exhibits featuring a well-rounded program and special displays on the history of medicine in the Philadelphia area, fractures, and manikin demonstrations on problems of delivery; (5) panel discussions on cardiovascular disease, cancer, emotional problems of menopause, hypertension, diabetes, arthritis, traumatic injuries; (6) presentation of the General Practitioner of the Year Award to an outstanding family doctor.

Grant to University of Kansas

The University of Kansas School of Medicine, Kansas City, was recently awarded a grant of $104,170 by the National Foundation for Infantile Paralysis for a study on what happens when different strains of polio virus invade the body of an experimental animal. The amount was part of a total of $4,527,064 awarded to 61 institutions.

The over-all goal is to support:

1. Research to solve problems of polio and other viruses, to improve methods of polio vaccination and to develop drugs helpful in treatment of polio and other virus diseases.

2. Research into treatment of polio after-effects, including the development of an iron lung controllable by the patient.

3. Regional polio respiratory and rehabilitation centers—where dynamic methods of treatment are developed.

4. A professional education program aimed at relieving shortages of workers in health fields and raising the quality of care for polio and other patients.

Scan the road, check the rear
Look to left and right.
You may not pull a bonehead play
But the other fellow might.

Jenkins-Keogh Hearings

Hearings on the Jenkins-Keogh plan, and on the general subject of taxation, will be held in Washington beginning on January 7, according to an announcement by Representative Jere Cooper, chairman of the House Ways and Means Committee. The group refused to consider Jenkins-Keogh bills in the session just ended.

The Jenkins-Keogh plan, strongly supported by the A.M.A., would allow self-employed persons to set aside a portion of their income in pension plans and defer payment of income tax on it until it is received back in the form of pensions. Corporations now may do this for their employees. The American Thrift Assembly, headquartered in Washington, has carried on the fight for the legislation this year.

A.M.E.F. Fall Campaign

The American Medical Education Foundation will launch an intensive fall campaign for contributions to the nation's medical schools. October and November have been selected as the months in which to appeal to physicians for individual donations.

To assist local committees the A.M.E.F. has prepared a new pocket portfolio with information cards and pledge envelopes. A new folder entitled "So They May Serve" has also been produced for use in local and state mailings. A new exhibit, first displayed at the A.M.A. convention in New York, is available from the foundation office. Featuring pictures of medical schools and gift checks to A.M.E.F., this exhibit illustrates reasons why medical schools should be privately supported.

In a progress report as of July 1, the foundation announced that the six million dollar mark of contributions from the medical profession had been passed earlier this year. The report also stated that so far in 1957 the A.M.E.F. income is 15 per cent higher than in the same period last year.

Physicians are urged to contribute generously to the foundation during the remaining months of 1957.

A.M.A. Prepares Liability Kits

The American Medical Association's Law Department is making available to each state medical society a packet of materials dealing with "medical professional liability." The kit will contain reprints from the *Journal of the A.M.A.* "Medicine and the Law" section dealing with such things as statutes of limitation, court decisions, and "res ipsa loquitur." Also enclosed will be the results of an opinion survey and a report on medical professional liability case histories—keyed to each state. Distribution began October 1.

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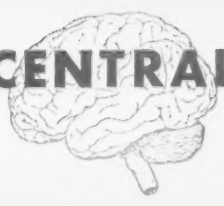

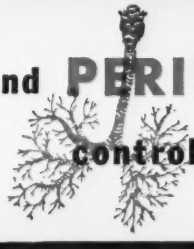

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Dihydrocodeinone bitartrate	1.33 mg.
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Ammonium chloride	70.0 mg.
Menthol	1.0 mg.
Chloroform	0.02 cc.
Alcohol	8%

Bottles of 16 fl. oz.

EXEMPT NARCOTIC

To Publish Medicolegal Material

To guide physicians and hospitals in the selection of appropriate medicolegal forms, the A.M.A.'s Law Department has compiled a series of six brief articles for the *Journal of the A.M.A.* These articles will appear weekly in the *Journal,* beginning about September 1. In addition, the law department will publish a booklet encompassing the material plus case citations and legal analysis for distribution about October 1.

Chief purpose of this material will be to provide up-to-date information and miscellaneous medicolegal forms which physicians and their attorneys may adapt for their own needs. Subjects to be covered: (1) consent to operations and other medical procedures; (2) patient's right to privacy; (3) confidential communications and records; (4) artificial insemination; (5) the physician-patient relationship; (6) autopsy.

In all cases, the law department strongly advises doctors to seek competent legal advice locally.

Cytologic Test Advocated

A nationwide program emphasizing an annual cytologic test for uterine cancer for all women is urged by Dr. Charles S. Cameron, former medical and scientific director of the American Cancer Society, as a means of reducing the cancer mortality rate.

"Foremost medical opinion is convinced that if every woman in the country had this examination every year, the number of deaths from uterine cervical cancer would be cut by as much as 90 per cent," Dr. Cameron writes in a 25-cent pamphlet, *Cell Examination—New Hope in Cancer,* published by the Public Affairs Committee, 22 East 38th Street, New York City.

"This would mean an annual saving of 16,000 lives," Dr. David A. Wood, president of the American Cancer Society, 1956-57, declares in the introduction to the pamphlet.

"To make any real dent in mortality figures," Dr. Cameron points out, "a campaign will have to be launched on a national scale that will be carried forward on several fronts at once.

"Hand in hand with a public education program to alert American women to the new lease on life this procedure affords . . . must go the enlargement of facilities for carrying out cell examination for uterine cancer. More cancer preventive and diagnostic centers must be established for persons who are apparently well.

"The cooperation of two kinds of physicians is needed for cyto-diagnosis," Dr. Cameron adds, "the pathologist who specializes in analyzing body tissue and fluids and all doctors who in any phase of their practice give female examination. . . . The role of the family doctor is equally important. He bridges the gap between the public and the pathologist.

"The biggest hurdle of all is facilities for screening slides. More pathologists will have to specialize in cytology, more cyto-technologists must be recruited, and more laboratories must be established to take care of the increased demand.

"The American Cancer Society and the National Cancer Institute are joining hands with pathologists and doctors to help enlarge cytologic facilities. They have both given grants to the National Committee for Careers in Medical Technology for the production and utilization of a recruitment film to induce more young people to enter the career of cyto-technologist."

Meanwhile, "women need not wait hopelessly until science discovers a cure for cancer. They can insure themselves against the scourge of at least one of the major types of cancer now by insisting on a cytologic examination for uterine cancer each year after they are 35," Dr. Cameron concludes.

"Every individual literally holds his own life in his hands as he makes the decision whether or not to bother about examinations. . . . When they accept it as a routine step in medical care, not only will a great victory have been won over one form of cancer but early detection of other kinds will have been made easier."

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Many factors contribute to this success – your leadership, a more aware public, improved methods and techniques of detection, diagnosis and treatment. There is every reason to expect this progress to continue to the point where half of those stricken by cancer will be saved. As yet, science does not have the know-how to save the other half.

That knowledge will be gained – and, indeed, the riddle of cancer itself, will one day be solved in the research laboratories. To continue to support this vital work, as well as to carry on its dynamic education and service programs, the American Cancer Society is seeking $30,000,000. We are again appealing to the public to "fight cancer with a checkup and a check."

The check is insurance for tomorrow. The insurance for today is largely in your hands, doctor. Fighting cancer with a checkup is our *immediate* hope for saving lives.

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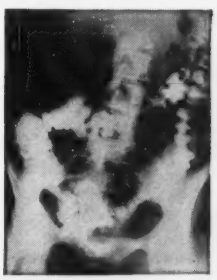

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TETRACYCLINE

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4 cc. plastic squeeze, dropper bottle containing ACHROMYCIN Tetracycline HCl (1%) 10.0 mg., suspended in sesame oil.

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Historical Material Needed

In preparation for the observance of The Kansas Medical Society's centennial anniversary, members of the Committee on History are attempting to collect all material of historical interest. Physicians who can contribute information, records, etc., are urged to send such to

Committee on History
Kansas Medical Society
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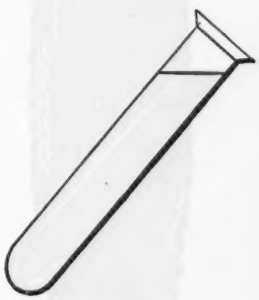

Physicians are quite aware of the rapidly growing appreciation of the role of dietary lipids in health and disease. Accumulating metabolic studies throughout the world indicate that serum cholesterol levels may be influenced more by the *kind* than by the *amount* of the dietary fat.

Unsaturated fats tend to depress serum cholesterol levels in many patients, whereas saturated fats may have the opposite effect. Medical references on this subject, as well as other findings concerning unsaturated fatty acids in nutrition, may be found in the book, "Vegetable Oils in Nutrition."

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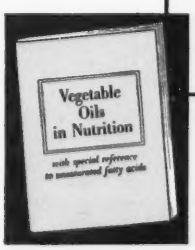
Fat	Fatty Acids as Percentage of Total Acids									Iodine Value	
	Saturated		Oleic		Linoleic		Linolenic		Arachidonic		
	Ave.	Range	Ave.	Range	Ave.	Range	Ave.	Range	Ave.	Average	Range
Butter	—	46-48	—	—	4.0	—	1.2	—	0.2	—	26-42
Coconut oil	—	75-88	—	5-8	—	1.0-2.5	—	—	—	—	7-10
Corn oil	13	11-15	—	23-40	56	46-66	—	0.0-0.6	—	126	113-131
Cottonseed oil	26	21-30	27	22-36	47	34-57	—	—	—	105	90-117
Lard	43	—	46	—	10	15.6	0.5	—	0.5 (2.1)	—	53-77
Linseed oil	—	6-12	—	13-31	—	10-27	—	30-64	—	—	170-204
Margarine	23	15-23	62	59-77	5.8	5-11	—	0.1-0.9	0	81	74-85
Olive oil	—	8-16	—	53-86	—	4-20	—	—	—	—	80-88
Peanut oil	17	14-22	54	44-65	29	20-37	—	—	—	98	90-102
Shortening	25	17-45	62	43-79	5	3-12	—	0.2-0.6	0-0.5	78	59-80
Soybean oil	15	11-18	25	18-58	55	28-62	5.1	0.3-10	—	130	100-143
Tallow (beef)	53	—	42	—	4	5.3	0.5	—	0.5	—	40-48



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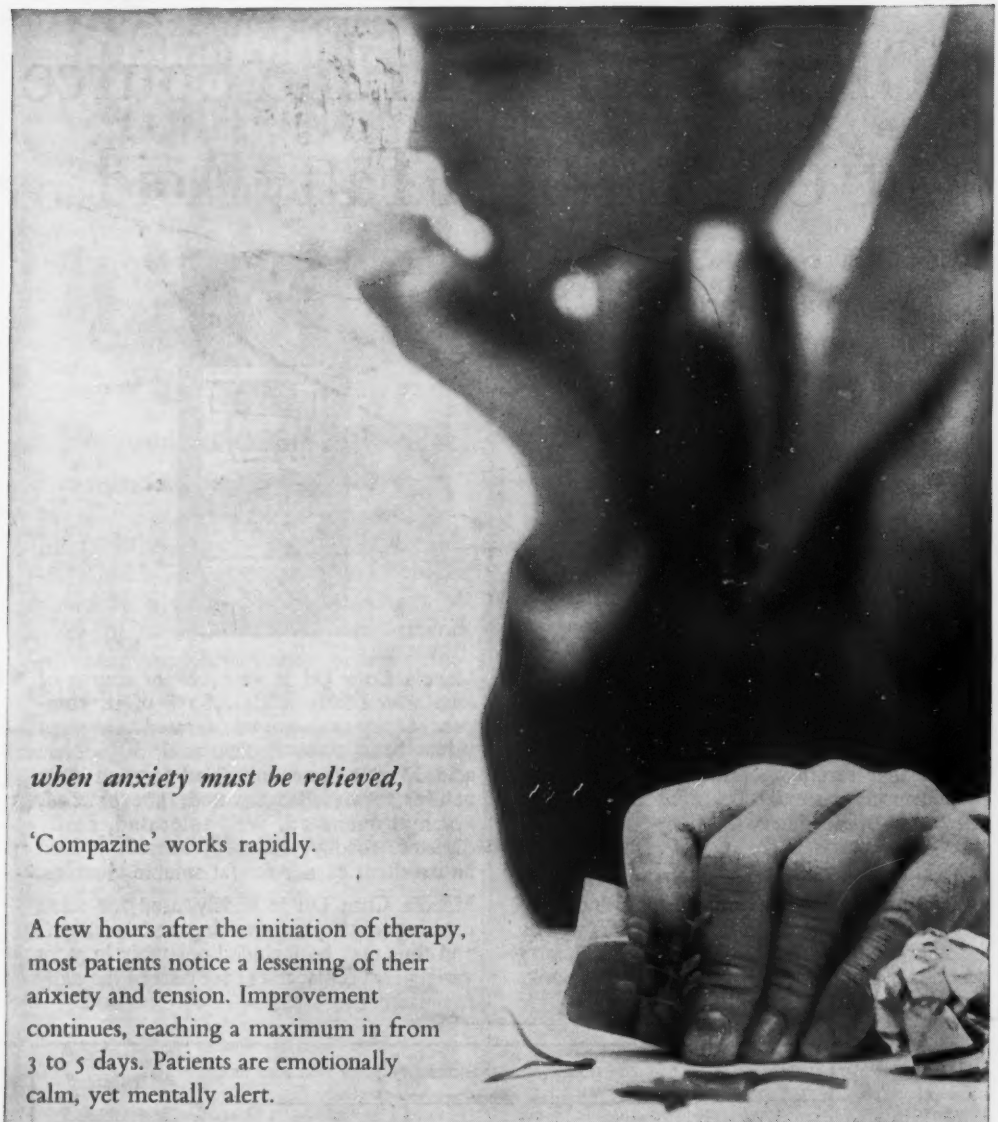

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